The cyclisation of some substituted benzylaminoacetonitriles.

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Award date:
1976

Awarding institution:
University of Bath

THE CYCLISATION OF SOME SUBSTITUTED BENZYLAMINOACETONITRILES

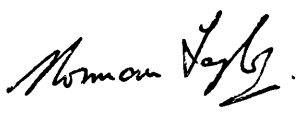
submitted by

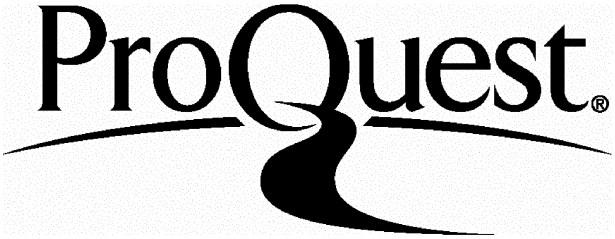
Norman Taylor

for the degree of Ph.D.

at the University of Bath, 1976.

The research has been carried out in the School of Pharmacy and Pharmacology of the University of Bath under the supervision of Dr. D.N. Harcourt, Ph.D., B.Pharm., M.P.S.





ACKNOWLEDGEMENTS

I wish to thank Dr. D.N. Harcourt for his encouragement and advice in the preparation of this thesis. I also thank Professor R.T. Parfitt for helpful discussion.

The author's sincere thanks are also due to Mrs. M. Thompson for typing the manuscript.

CONTENTS

SUMMARY

A series of new 4-methoxybenzylaminoacetonitriles has been prepared and characterised. These have been cyclised with concentrated sulphuric acid and a new non-classical mechanism is postulated. Depending on the nature and position of the substituent groups on the nitrile the following classes of compound have been prepared:

4-oxo-tetrahydroisoquinolines

3-imidazolines

3, 3-disubstituted tetrahydroisoquinolines

N-substituted tetrahydroisoquinolines

2-benzazepines

The mechanism postulated satisfactorily explains the formation of all the above classes of compound and also the formation of certain 3,3-disubstituted-4-oxo-tetrahydroisoquinolines previously reported [1].

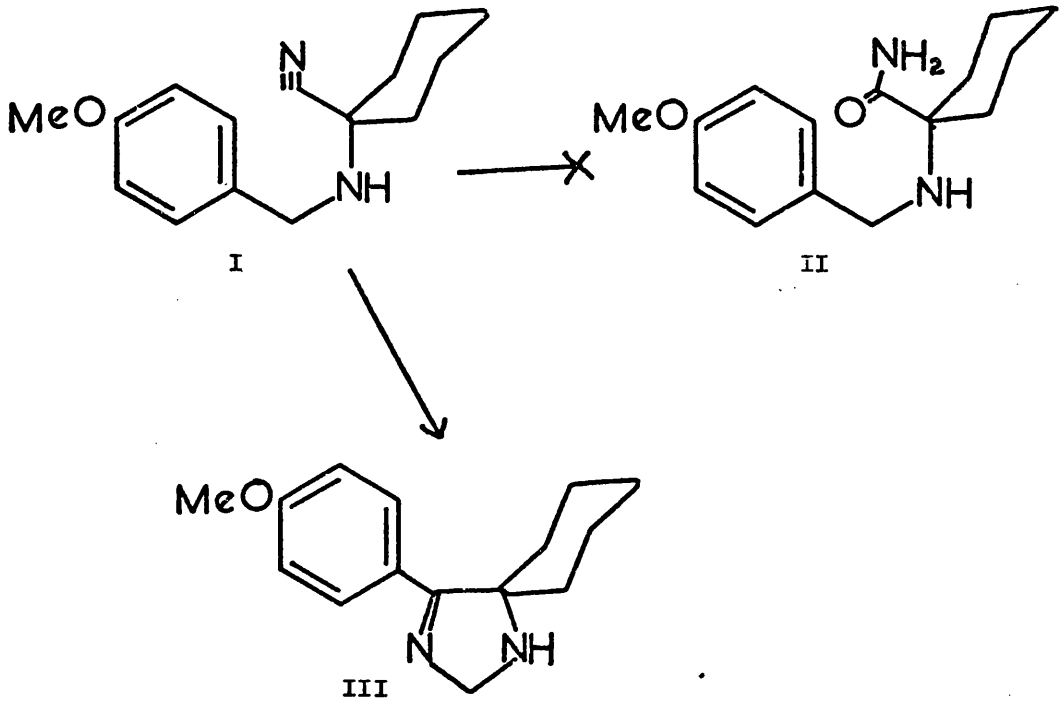
Structural assignments have been made by means of elemental analysis and infra red spectroscopy; extensive use has been made of nuclear magnetic resonance and mass spectroscopy.

Several new compounds have been tested for biological activity.

INTRODUCTION

Work by Harcourt and Waigh [1] describes the synthesis of 3,3-disubstituted-4-oxo-tetrahydroisoquinolines from 3,4-dimethoxybenzylaminoacetonitriles, postulating a classical ring closure *para* to the 3-methoxyl group. Further work has shown that an alternative mechanistic pathway may be more likely and it is the purpose of the present work to substantiate this theory.

The initial stimulus was provided by an attempt to hydrate 2-(4-methoxybenzylamino)-2-spirocyclohexylacetonitrile (I). Instead of the expected amide (II), a 3-imidazoline (III) was produced.



The mechanism proposed for the formation of III involves the production of a spiro intermediate which re-arranges to give an iminium ion. The fate of the iminium ion is then decided by the

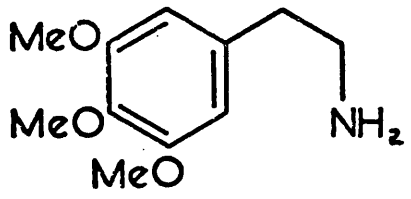
proximity of differing nucleophiles. Such a mechanism is, in part, reminiscent of a Hayashi Re-arrangement [2-6].

Of the five classes of compound resulting from the cyclisations carried out, least published work is available concerning the 3-imidazolines . The chemistry and pharmacology of certain trifluoromethyl-3-imidazolines has been studied [e.g. 7, 8] and Russian workers [e.g. 9] have shown great interest in the preparation of stable iminoxyl radicals but these were not considered to be in the context of the present work.

At the other extreme, a vast amount of work has been published concerning the chemistry of simple isoquinolines. A brief survey has been made of some aspects of this work and is presented as a separate section.

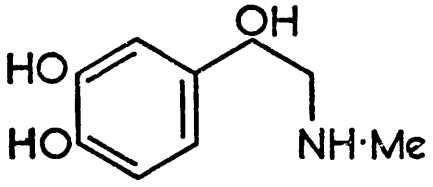
Isoquinolines

The isoquinoline ring system is widely distributed in nature[10]. Isoquinoline alkaloids vary greatly in complexity and the number of simple tetrahydroisoquinolines i.e. with one aromatic nucleus, is relatively small. Several simple isoquinoline alkaloids have been isolated from various species of Cactus, particularly Anhalonium lewinii which is cut into slices and dried to give "mescal buttons". "Mescal buttons" are either chewed or extracted with alcohol to produce a drink, the effect of which is the disturbance of normal mental function with concomitant hallucinations and euphoria, and mydriasis accompanied by bizarre colour perceptions. These physiological effects are due mainly to the β-phenylethylamine mescaline [11] IV.



IV

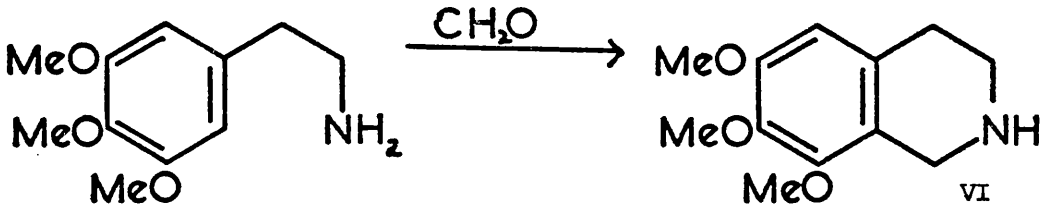
A number of substituted β-phenylethylamines have been isolated from plant material in recent years [e.g.12,13] and because of their structural resemblance to adrenaline V are of obvious physiological and pharmacological interest.



V

Early workers in this field[14, 15] recognised such compounds as possible biosynthetic precursors of the simple isoquinoline alkaloids.

For example, mescaline condensed with formaldehyde would give anhalinine VI.



VI

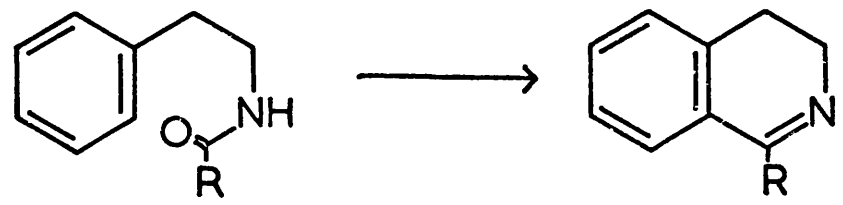
For many years isoquinoline chemistry was chiefly concerned with 1- and 2- substituted derivatives. This arose because the available methods of synthesis were not readily adaptable to the preparation of large numbers of 3- and 4- substituted products. These traditional methods have been reviewed by Manske[16] and Gensler[17].

With few exceptions isoquinoline syntheses may be divided into three categories, according to the intermediates required.

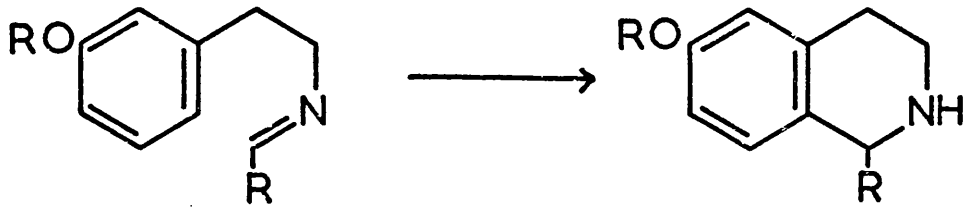
Category 1 - cyclisation of a phenylethylamine derivative.

This is the most important historically and includes the Bischler-Napieralski and Pictet-Spengler syntheses together with their modifications.

Bischler-Napieralski Synthesis (1893)

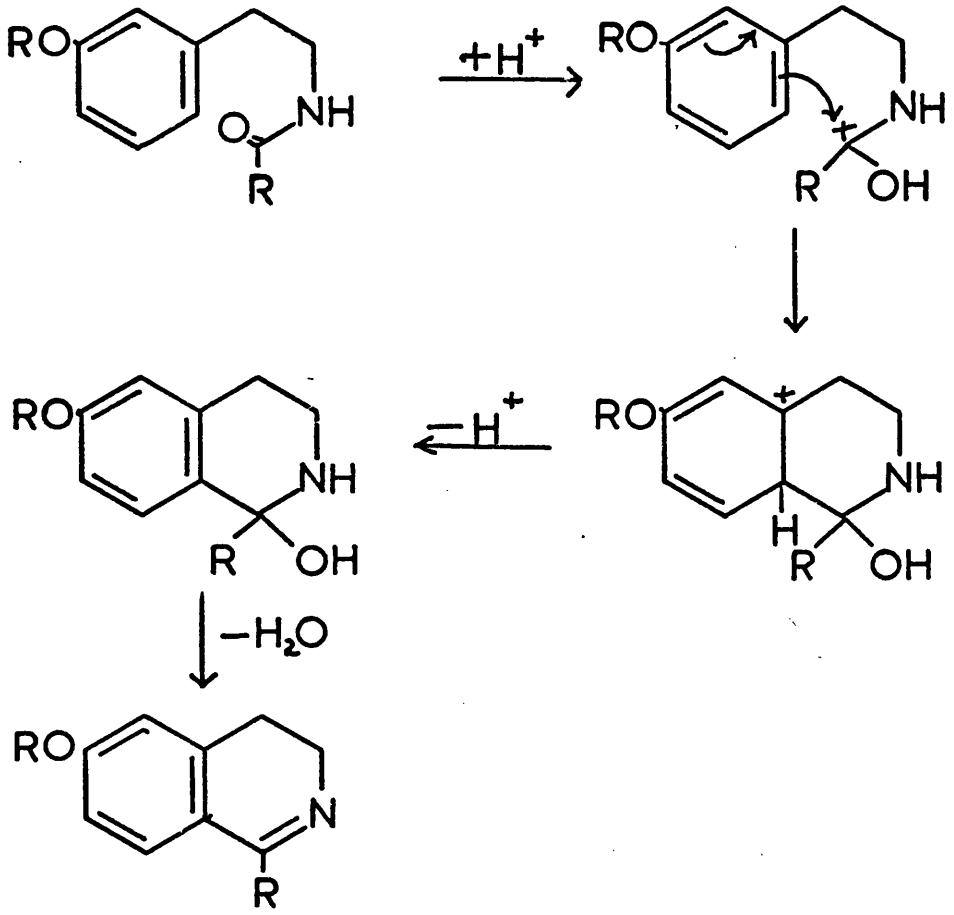


Pictet-Spengler Synthesis (1911)

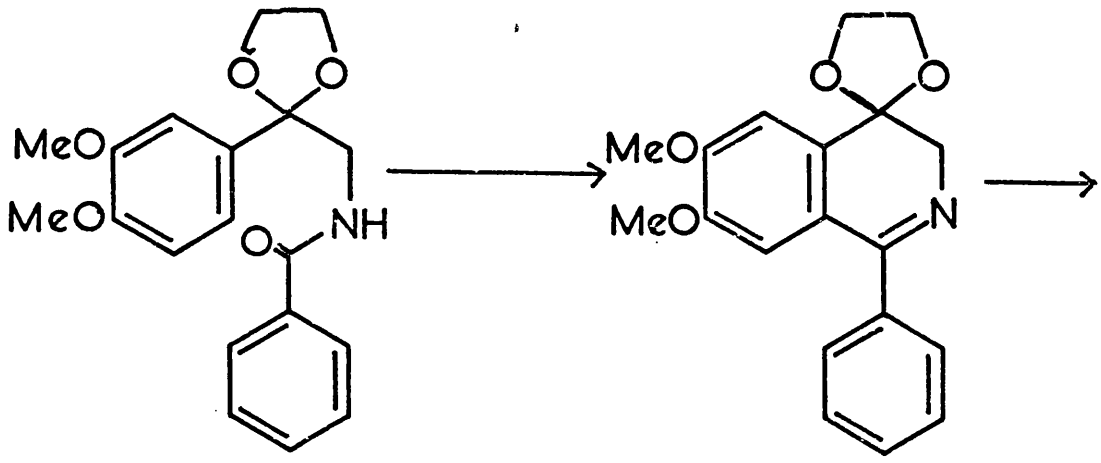


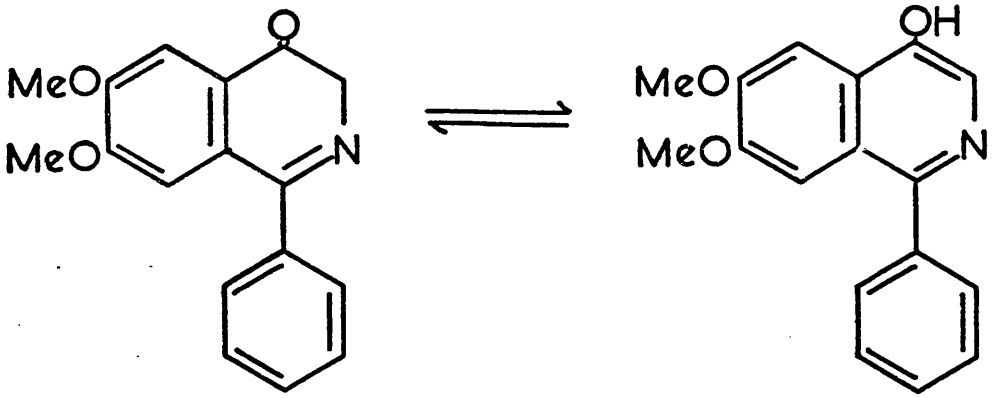
Both of these methods have been frequently employed, generally to give 1-substituted isoquinolines, and have been reviewed[18,19].

Ring closure is effected in acid solution which may be disadvantageous if acid labile groups are present.

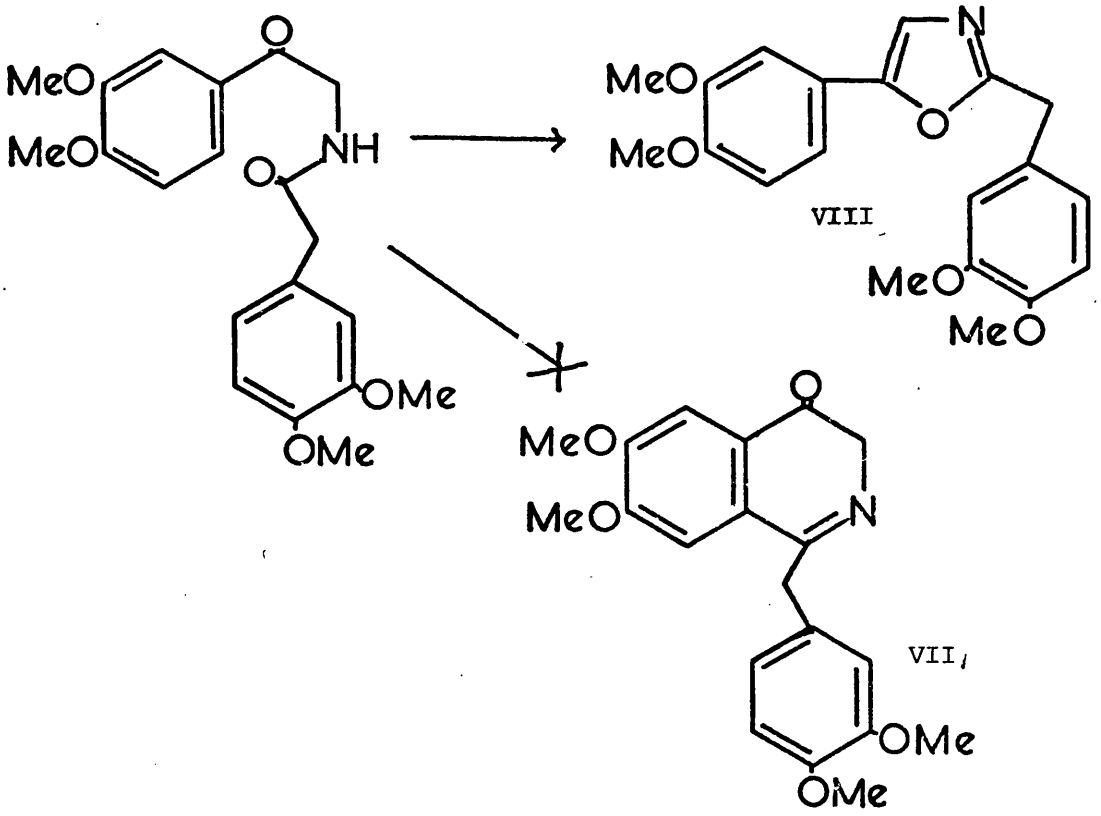


Itoh and Sugasawa[20] elegantly overcame the necessity of an acid medium by carrying out the cyclisation of a ketal with phosphorus pentoxide in pyridine solution.



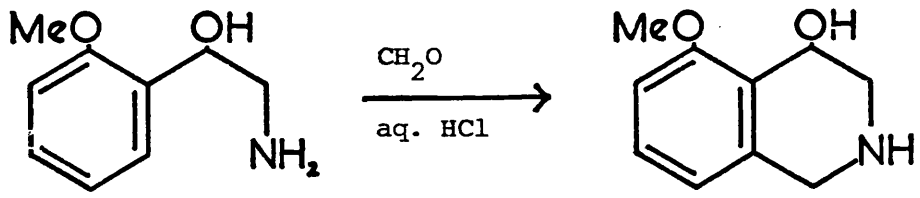


The necessity to protect the carbonyl function is well illustrated by the work of Buck[21]. A reaction designed to produce a 4-oxo-isoquinoline VII was later shown[22] to have produced an oxazole VIII when cyclised by the usual Bischler-Napieralski method.

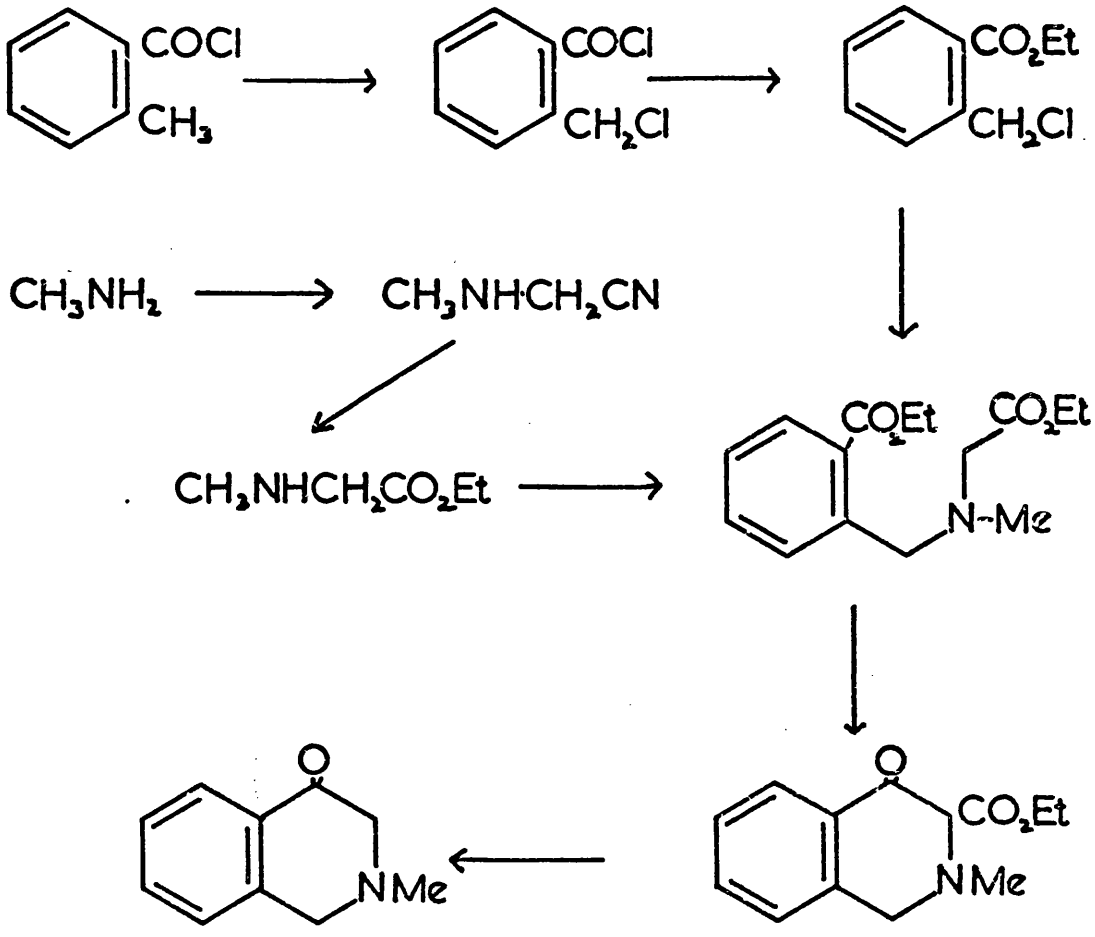


The modification of the Bischler-Napieralski synthesis by Pictet and Gams[23] employs a β-hydroxy-β-phenylethylamide. This readily undergoes dehydration when heated with the acid catalyst and the styrylamide so formed is cyclodehydrated to give the fully aromatic

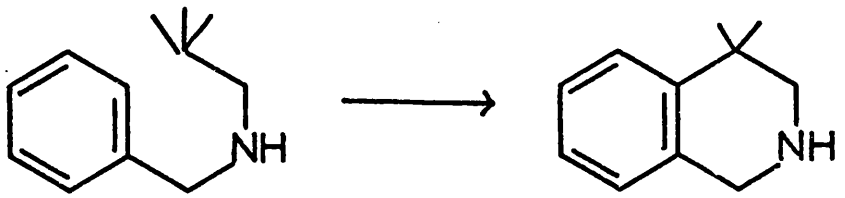
isoquinoline. Where a 4-hydroxyisoquinoline is required the more gentle conditions of a Pictet-Spengler cyclisation are preferred[e.g.24].



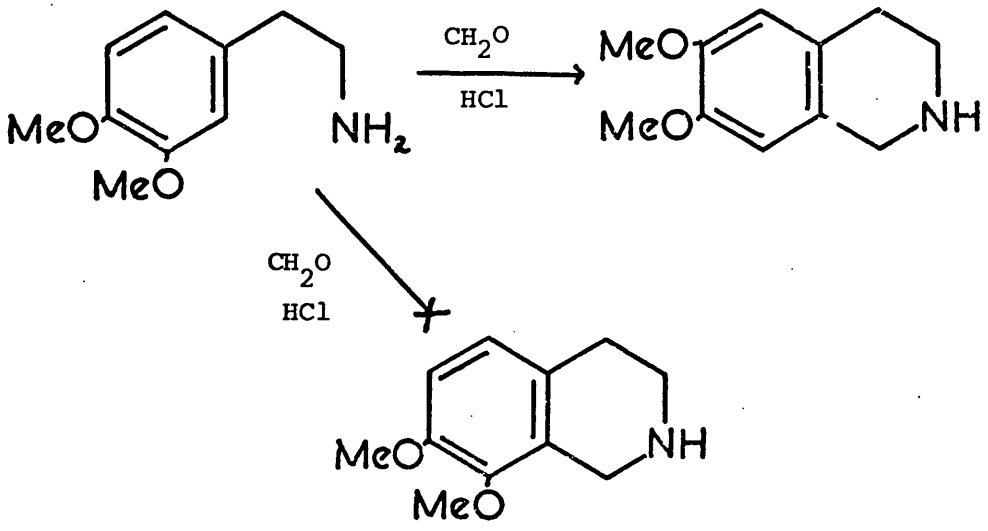
Category 2 - This type of isoquinoline synthesis depends on the cyclisation of ortho disubstituted benzene derivatives. It includes many published reactions, the limitations generally being the difficulty in preparing suitable starting material. This is well illustrated by the work of Hinton and Mann[25] in preparing a 4-oxo-isoquinoline.



Category 3 - The cyclisation of a benzylamine or benzalamine derivative is one of the more attractive methods of isoquinoline synthesis, certainly with regard to accessability of starting materials.



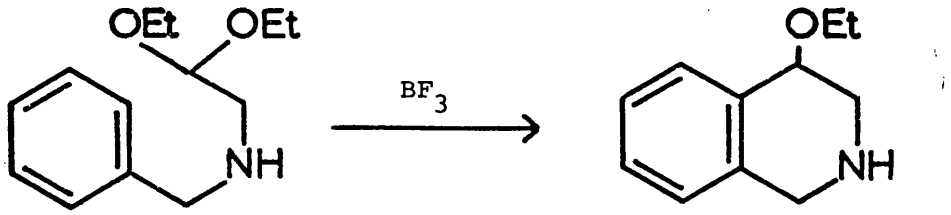
Great emphasis has been placed on the difficulty of this type of cyclisation. A list of failures is reported by Gensler in a review[17] and Dey and Govindachari[26] devoted a paper entirely to negative results from this approach. However, for many years, this now classical Pomeranz-Fritsch synthesis was the only known synthetic route to 7,8-dimethoxyisoquinolines, an orientation impossible to obtain directly by either Bishchler-Napieralski or Pictet-Spengler cyclisations.



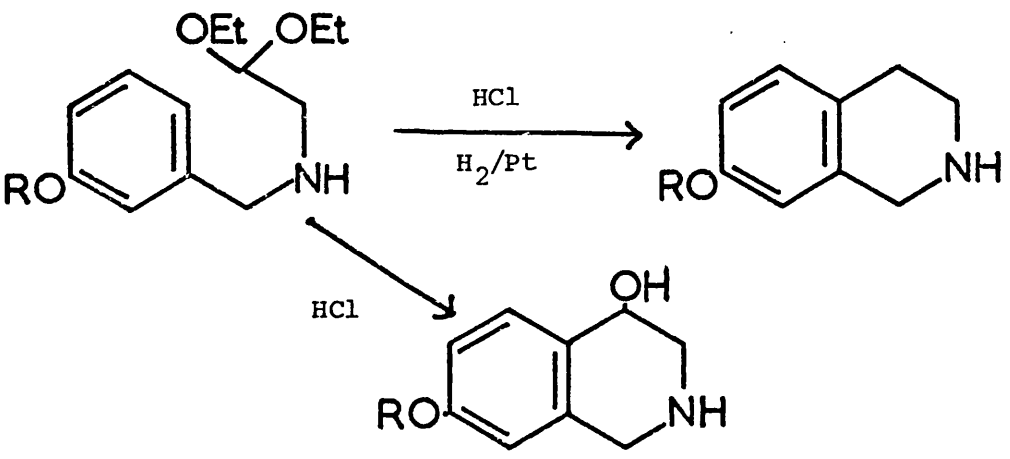
Essentially the synthesis consists of converting an aromatic aldehyde into a Schiff's base with an aminoacetal followed by cyclisation in sulphuric acid. The results obtained have varied greatly. Where the acid concentration has been too low the Schiff's base has been hydrolysed back to its components whilst too high a concentration of acid has led to extensive decomposition.

Many attempts were made to overcome this problem, initially with only limited success e.g. Bevis[27] and co-workers employed polyphosphoric acid instead of sulphuric acid as the cyclising agent but with one exception, yields were less than 20% of the theoretical.

The first really successful cyclisation was by Quelet and Vinot[28] who used boron trifluoride as the cyclising agent.



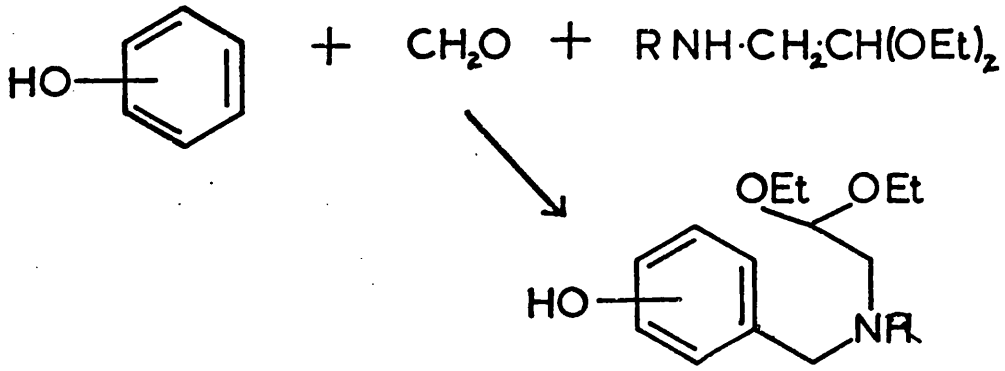
The fact that this reaction is less successful when the benzene ring is oxygenated is complemented by the work of Bobbitt[29,30], who successfully used 6N. hydrochloric acid as the cyclising agent providing an oxygen atom was present in the position ortho or para to the point of ring closure.



A modification of this synthesis by Jackson and co-workers[31] consists of tosylating the benzylaminoacetal prior to ring closure with 6N hydrochloric acid in dioxan in the dark in an atmosphere of nitrogen.

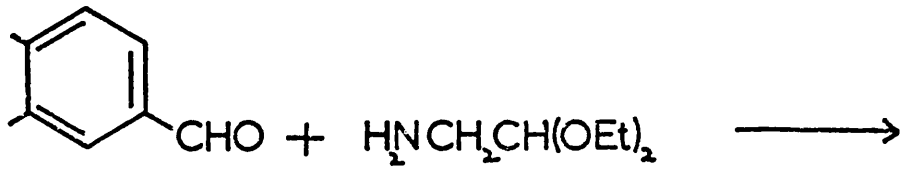
The preparation of the required benzylaminoacetal has been achieved by four main routes.

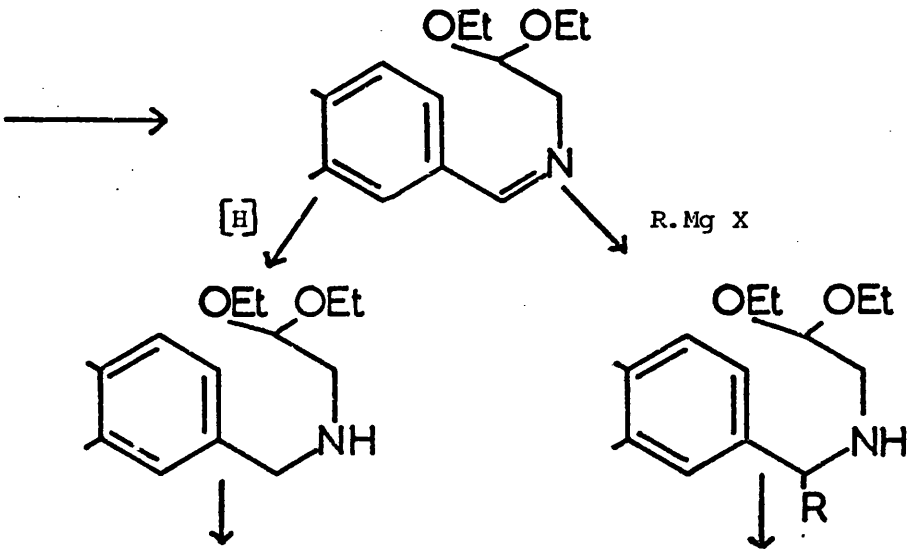
a) via a Mannich reaction[32]. Phenols may be condensed with formaldehyde and a secondary aminoacetal to give the required starting material.



A major disadvantage of this approach is that the Mannich condensation may take place ortho or para to the phenolic hydroxyl group giving a mixture of isomers. Guaiacol gives rise to 8-hydroxy-7-methoxy and 6-hydroxy-7-methoxyisoquinolines.

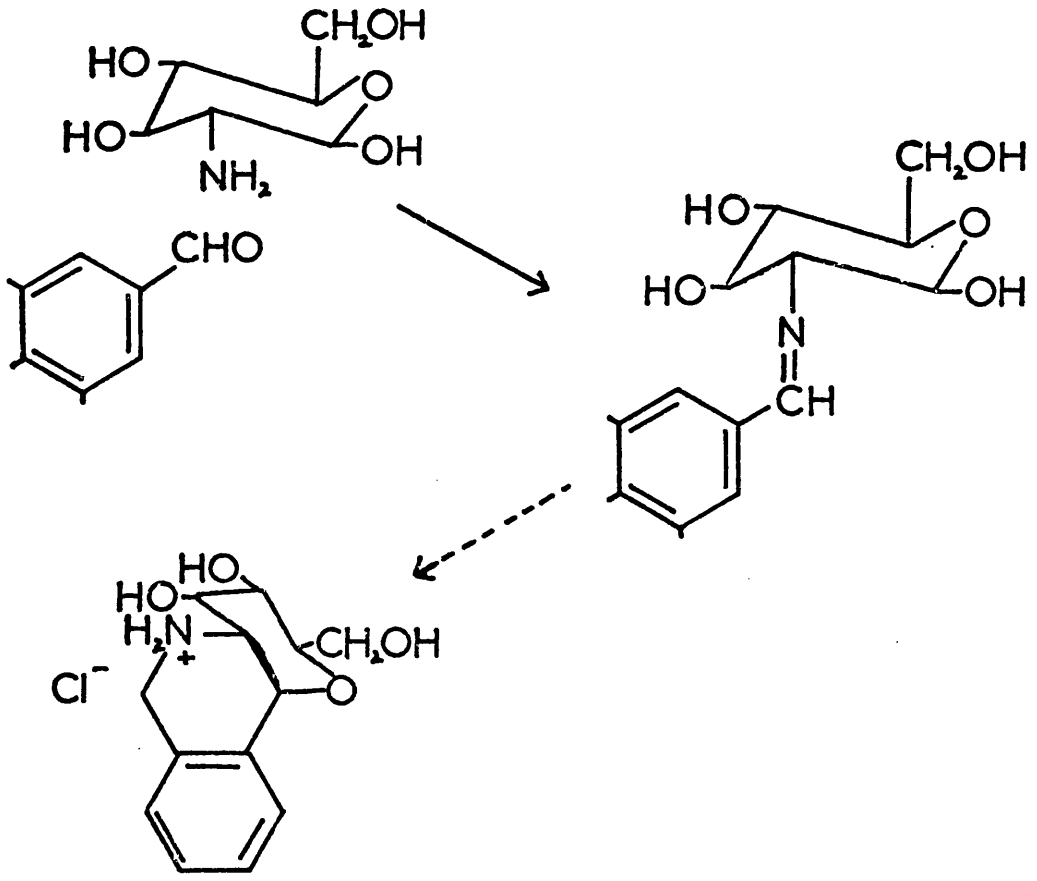
b) from aromatic aldehydes. A substituted benzaldehyde may be condensed with an aminoacetal to produce a Schiff's base. This may be reduced to the benzylaminoacetal, giving, on cyclisation a simple tetrahydro isoquinoline or reacted with a Grignard reagent leading to a 1-substituted compound.





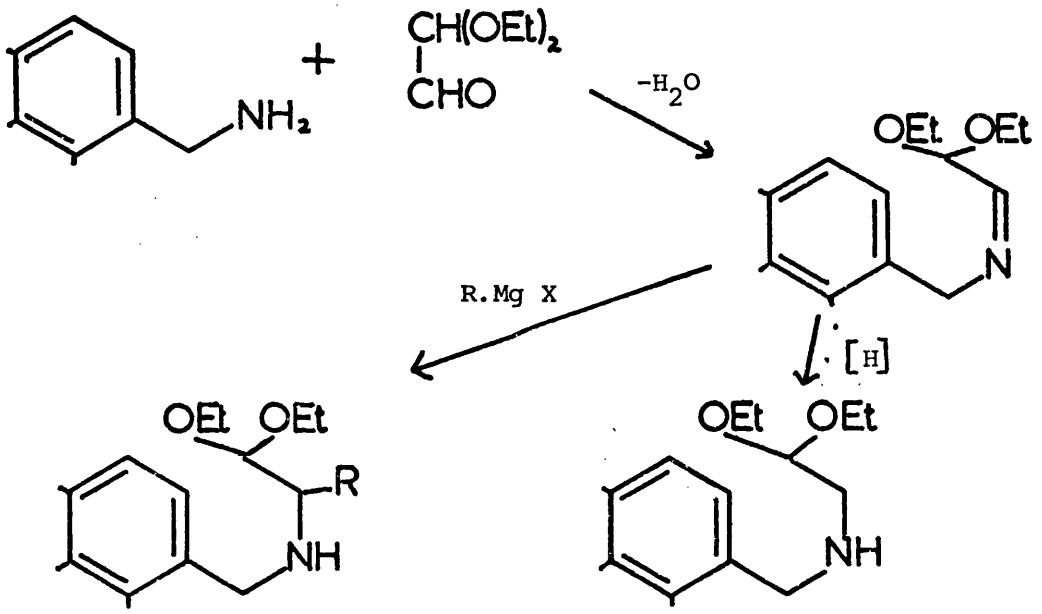
The many methods of reducing the Schiff base have been summarised by Emerson[33].

An interesting variation[34] has been the use of D-glucosamine to form the Schiff base, cyclisation of which gave a tetrahydro-isoquinoline attached to a glucose moiety.



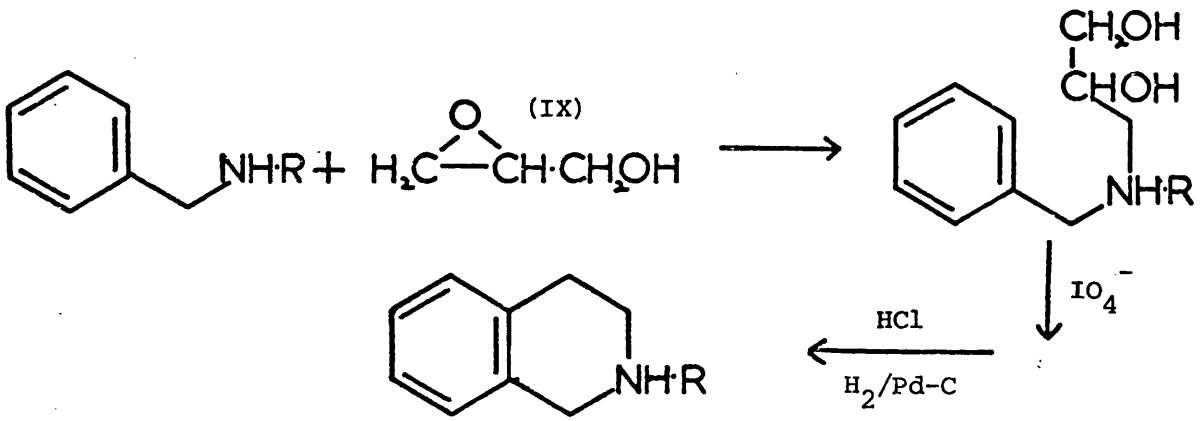
c) from ketones. This offers a route comparable to b) for the preparation of 1-substituted tetrahydroisoquinolines but is of greater difficulty experimentally because of the low reactivity of ketones with primary amines. The experimental difficulties have been overcome in the case of simple acetophenones by carrying out the reaction in absolute alcohol[35] and in other cases by heating the reactants together without a solvent at 105-125° under nitrogen[36]. Possibly a better method is to convert the ketone to a substituted benzylamine via the oxime[37] and to proceed as in d).

d) from benzylamines. Benzylamines have long been reacted with bromoacetaldehyde diethyl acetal to form starting materials for tetrahydroisoquinoline syntheses[e.g.22,38]. Similarly the condensation of glyoxal semiacetal[39] with benzylamine allows for the synthesis of 3-substituted tetrahydroisoquinolines.



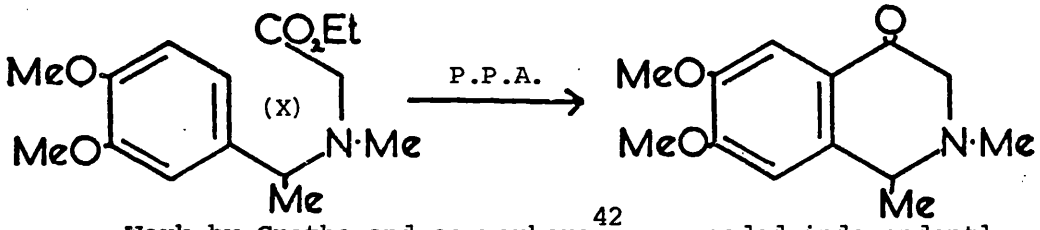
The major difficulty in the latter method has been the preparation of intermediates which involve multistage syntheses and which are, in some cases, difficult to handle.

A later improvement was the use of glycidol(IX)by Frank and Purves[40,40a].

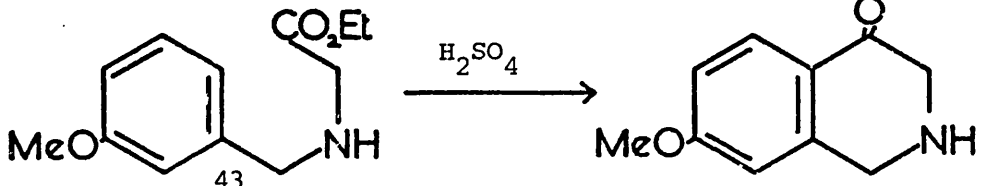


The obvious advantage is the commercial availability of pure, stable intermediates and the fact that a secondary amine may be used.

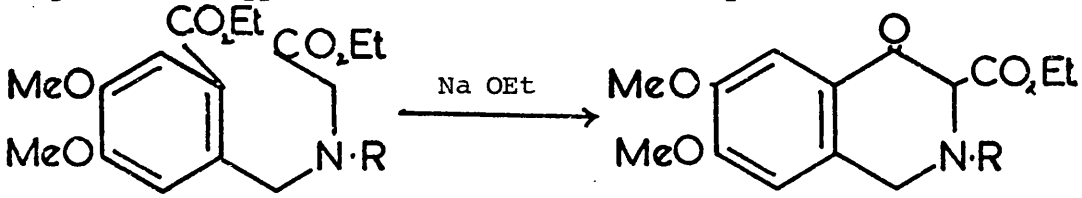
A major development in the synthesis of 4-keto-tetrahydroisoquinolines was the work of Kametani and Fukumoto[41]. These workers cyclised an N-benzylglycine ester(X)with polyphosphoric acid.



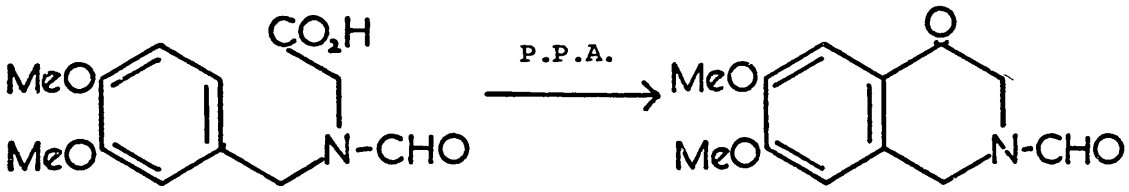
Work by Grethe and co-workers[42] proceeded independently using sulphuric acid as the cyclising agent.



Grethe[43] reported unsatisfactory yields in the preparation of 6,7-dimethoxyisoquinolines by this method and favours a Dieckmann cyclisation approach for this substitution pattern.



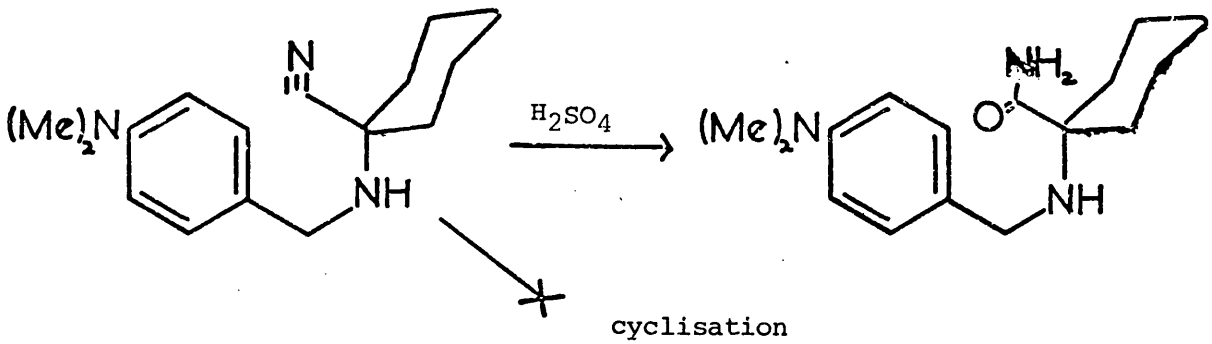
Without reference to the work of Kametani, other Japanese workers[44,45] have reported the cyclisation of N-benzylglycine derivatives.



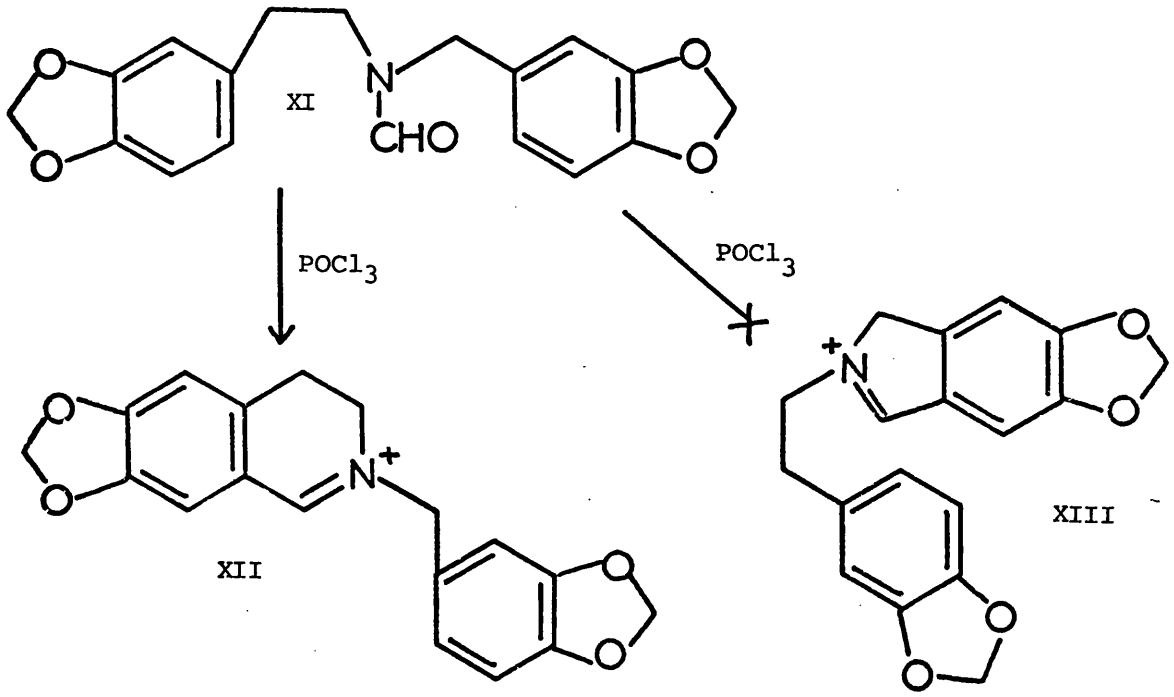
The work of Harcourt and Waigh[1] together with the present work shows that cyclisation of benzylaminonitriles has many advantages (and some disadvantages) over other methods reported. Depending on the pattern of substitution on the nitrile, cyclisation may be effected to give 4-oxo-tetrahydroisoquinolines, tetrahydroisoquinolines, 3-imidazolines or 2-benzazepines.

Almost inevitably, cyclisations of benzylamine derivatives are acid catalysed, since they involve attack upon a phenyl ring. Thus the key intermediate in any cyclisation of this type may be considered to be a carbonium ion, formed either by protonation or by complex formation with a Lewis acid resulting in an intra-molecular Friedel-Crafts reaction. Cyclisation would therefore be facilitated by electron donating groups ortho or para to the point of ring closure, and hindered by a reverse effect. Thus the cyclisations carried out by Bobbitt[29] gave satisfactory yields only when an oxygen substituent was present ortho or para to the point of ring closure.

The use of boron trifluoride[28] shows the reverse effect, presumably because the more powerful oxygen lone pair co-ordination with the catalyst reverses the electron donating properties of the oxygen atom. A comparable effect was noted in the present work when the aromatic ring carried a dimethylamino group instead of a methoxyl. Cyclisation failed and an amide was produced.



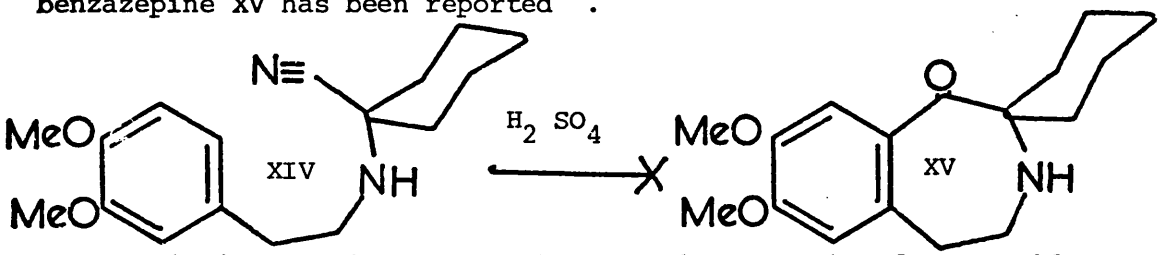
That the nitrogen of the benzylamine residue is separated from the ring under attack by only one carbon atom as compared to two in the case of Bischler-Napieralski and Pictet-Spengler syntheses provided the basis of early argument explaining the difficulty of isoquinoline synthesis from benzylamines. Malan and Robinson[46] compared the situation with the Bischler-Napieralski cyclisation of the formyl derivative of N-piperonyl-homopiperonylamine XI, which gave exclusively the N-piperonylisoquinolinium salt XII, rather than an isoindole XIII.



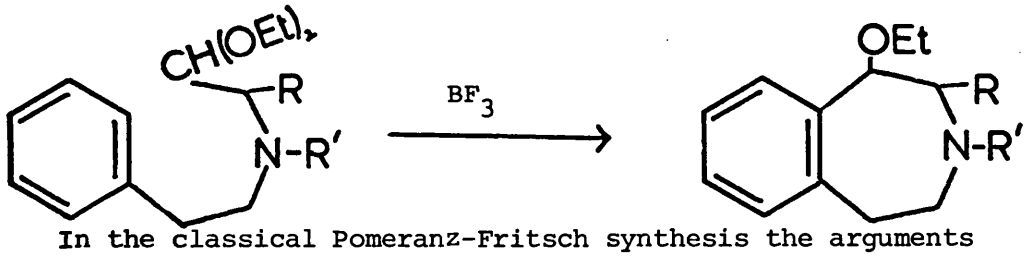
Whilst the deactivating effect of the positive nitrogen would have greater effect on the benzylamine moiety it is only an inductive effect and greatly weakened by transmission through two sigma bonds.

It would be expected that this adverse effect be readily overcome by the powerful conjugative effect of the alkoxy group. This cannot then be accepted as an adequate explanation for preferential cyclisation to the isoquinoline rather than the isoindole. A more likely explanation may lie in the greater strain inherent in five

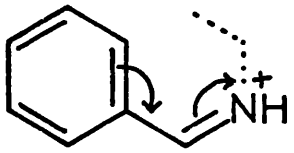
membered rings. Similarly, the failure of 2-[2-(3,4-dimethoxyphenyl) ethylamino]-2-spirocyclohexylacetonitrile XIV to cyclise to a benzazepine XV has been reported[47].



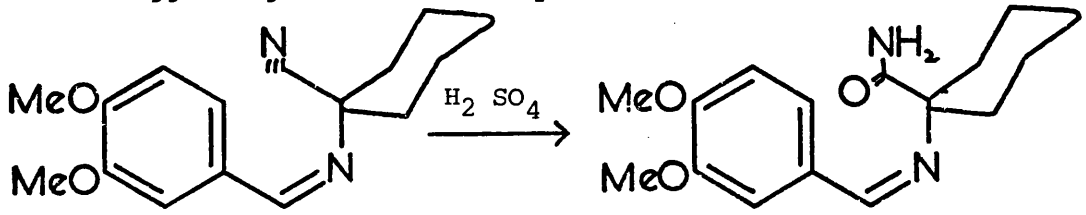
It is interesting to note however that acetals of comparable structure will give benzazepines with boron trifluroide[48].



In the classical Pomeranz-Fritsch synthesis the arguments concerning electron withdrawal are stronger since the nitrogen atom is conjugated with the ring.



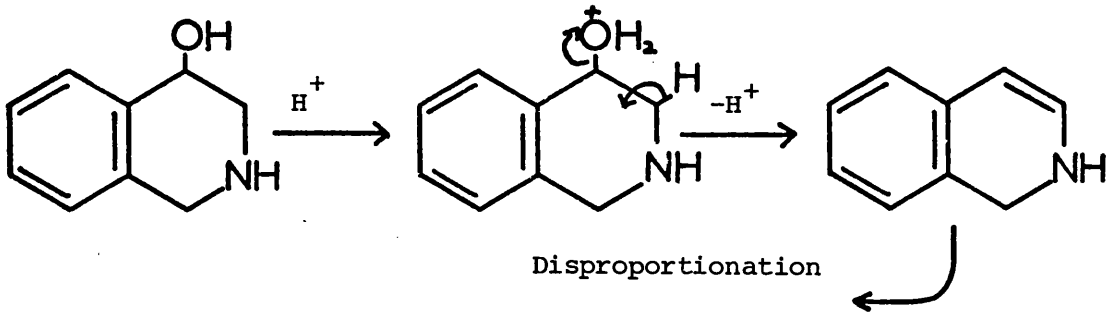
Nitriles of comparable structure, even when the ring is activated by two methoxyl groups will not cyclise but give only the amide[49] suggesting that acetals may be the more reactive.



Other less obvious factors are no doubt also involved. The choice of cyclising agent is always of great importance as is the oxidative state of the hetero ring of the isoquinoline. These two variables may have been responsible for many reported failures.

The pioneers of isoquinoline chemistry produced 3,4-dihydroisoquinolines, tetrahydroisoquinolines or fully aromatic

compounds. In contast, many later unsuccessful cyclisations were designed to produce 1,2-dihydroisoquinolines, now recognised as being unstable and/or very reactive[50,51]. This also applies to the 4-hydroxytetrahydroisoquinolines which readily dehydrate to give 1,2-dihydroisoquinolines.



Disproportionation

Polymerisation

Oxidation

In view of their ease of formation and their close resemblance to naturally occurring compounds having physiological activity a structure activity study would be worthwhile.

Aminonitriles

Aminonitriles are the most important synthetic route for the preparation of aminoacids [53]. They have also been used as intermediates in the synthesis of a number of heterocycles e.g. imidazoles[54], oxazoles[55], thiazoles[56], pyrazines[57], 4-oxo-tetrahydroisoquinolines[1] and benzodiazepines[58]. The present work extends the number of heterocycles prepared from such intermediates to include tetrahydroisoquinolines, 3-imidazolines and 2-benzazepines.

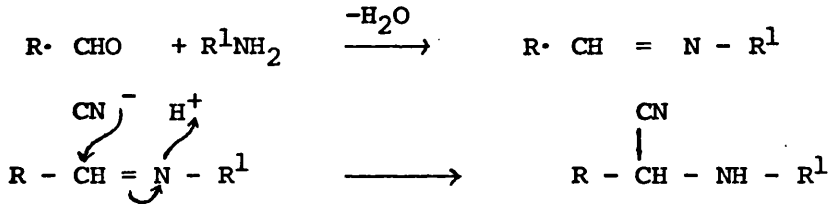
The Strecker synthesis[59] was the first preparation of an aminonitrile, using acetaldehyde, ammonia and hydrogen cyanide as an intermediate in the synthesis of alanine. When a primary amine group is required in the product, ammonia or an ammonium salt must be employed. Holland and Nayler[60], in preparing 1-amino-3-methylthiobutyronitrile stress the use of excess ammonia. Cocker[61] and co-workers recommend the use of twice the theoretical amount of ammonia, whilst Pierson[62] passed gaseous ammonia into a cyanohydrin. A rather surprising synthesis by Barger and Coyne[63] reacts a carbonyl compound, dissolved in ether, with the cyanide and ammonium chloride in an aqueous phase. Catch[64] and cc-workers used anhydrous hydrogen cyanide to introduce the nitrile group.

The first reported use of amines in a Strecker type reaction is by Bersworth[65] who reacted aliphatic amines with aldehydes and an alkali cyanide to produce, after hydrolysis, α-aminoacids. Similarly, Harcourt and Waigh[1] prepared a series of aminonitriles in good yield by reacting veratylamine hydrochloride with a carbonyl compound and excess potassium cyanide in aqueous or

aqueous alcoholic solution. This method was followed in the present work, generally producing the required nitrile in good yield.

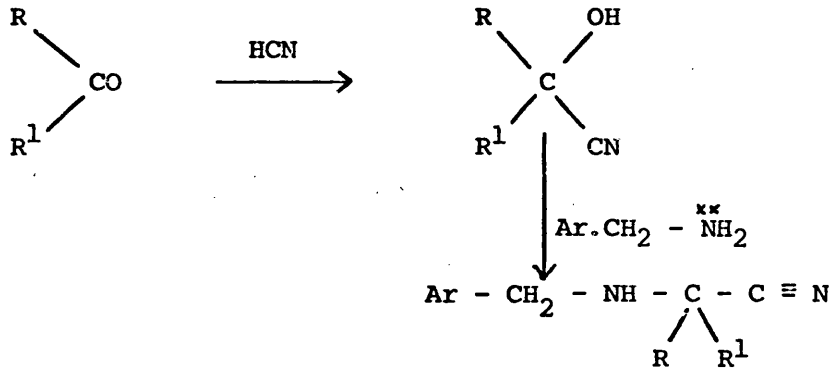
It is recognised that a variety of alternative methods are available but they are considered to be needlessly elaborate and often give inferior yields.

The mechanism of the reaction has not been satisfactorily explained. Aldehydes may be considered to react with the primary amine forming a Schiff base which in turn reacts with hydrogen cyanide, presumably by nucleophilic attack on the electron deficient carbon.



However, in view of the slow reaction between primary amines and ketones, together with the fact that the reaction proceeds satisfactorily with secondary amines suggests that these should be an alternative mechanism.

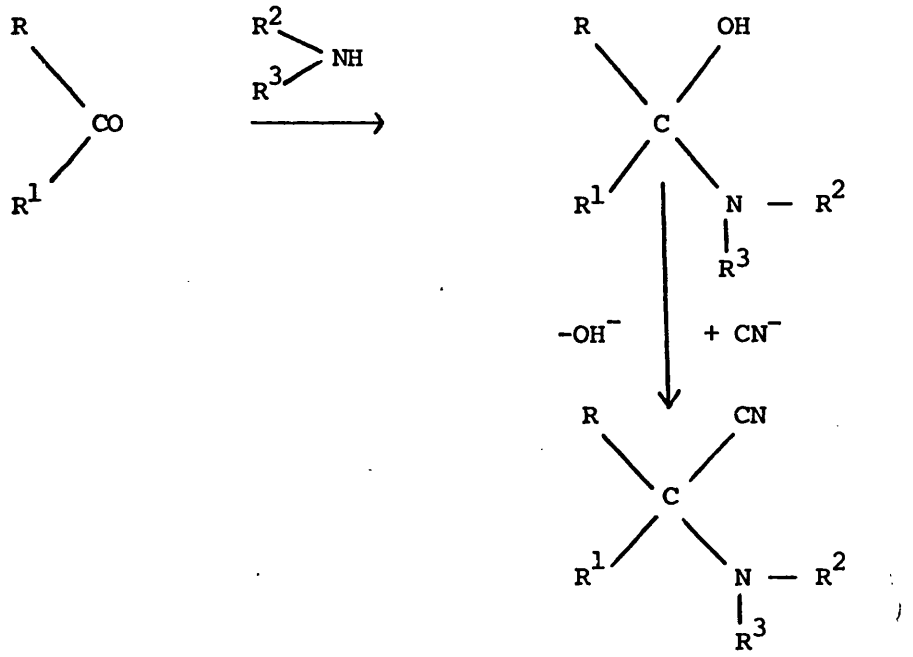
A possibly more acceptable mechanism is via cyanohydrir formation followed by nucleophilic attack by the lone pair of electrons of the nitrogen atom.



This latter mechanism was regarded as unlikely by Stewart and Li[66] who supported their argument with a study of the rate constants for the reaction of acetone cyanohydrin with diethylamine in solution in

acetone and alcohol. However, they do not offer any explanation for the reactivity of ketones in this context.

Another possible mechanism to explain the reactivity of ketones in this type of reaction is the formation of an intermediate amino-alcohol followed by nucleophilic attack by the cyanide ion.



The observed result may well be due to a combination of the above reactions.

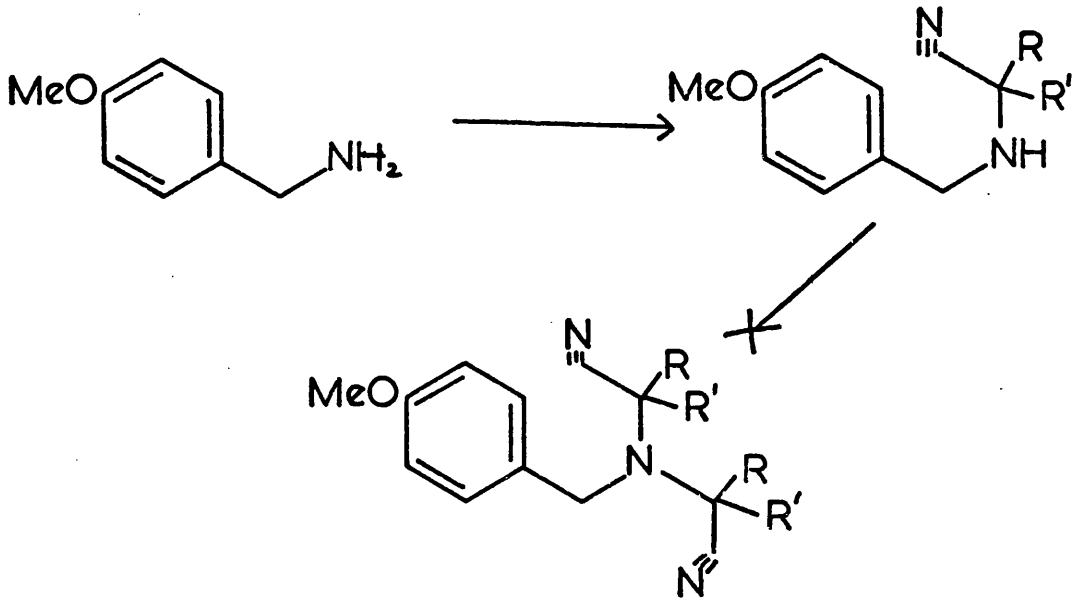
In the present work, an aqueous or aqueous alcoholic solution of the amine hydrochloride and the carboxyl compound was treated with potassium cyanide and after stirring for up to two days the product was isolated without difficulty, generally in good yield. The method proved generally applicable to primary and secondary benzylamines, and aldehydes and ketones.

Where the nitrile produced was an oil, certain difficulties were sometimes experienced in purification. Cook and Cox[67] express the opinion that "no aminonitrile preparation in which the product was not isolated by distillation can be regarded with complete confidence". In the present work decomposition invariably resulted from attempted

distillation. Attempts to produce a crystalline hydrochloride were equally unsuccessful with some compounds, a retro-Strecker reaction regenerating the original amine hydrochloride. In characterising such compounds, the author had to rely on spectroscopy alone as a sufficiently high state of purity could not be achieved for elemental analysis.

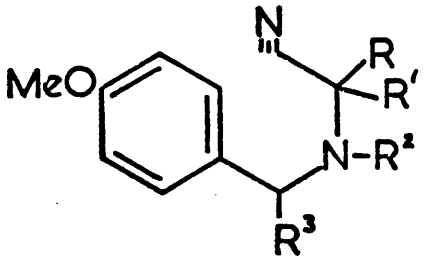
The reaction proceeded at room temperature except where formaldehyde was used (as paraformaldehyde) when the reaction was carried out on a steam bath.

It was noted that where a primary amine was used there was no evidence of disubstitution even when an excess of formaldehyde had been used[68].



The aminonitriles prepared in the present work are divided into groups according to the expected product of cyclisation.

GROUP 1 - precursors of 3-imidazolines.



R	R^1	R^2	R^3	% yield
$-(CH_2)_5-$		H	H	I*
$-(CH_2)_4-$		H	H	84% XVI
Et	Et	H	H	82% XVII
Et	Me	H	H	87% XVIII
Me	Me	H	H	72% XIX
Me	H	H	H	87% XX
H	H	H	H	90% XXI
$-(CH_2)_5-$		Me	H	73% XXII
$-(CH_2)_4-$		Me	H	82% XXIII
Me	Me	Me	H	90% XXIV
$-(CH_2)_5-$		Bz	H	56% XXV
$-(CH_2)_5-$		DMeOBz	H	52% XXVI
$-(CH_2)_5-$		ClBz	H	57% XXVII
$-(CH_2)_5-$		H	Bz	67% XXVIII

Bz = Benzyl

DMeOBz = 3.4 dimethoxybenzyl.

ClBz = 4-chlorobenzyl

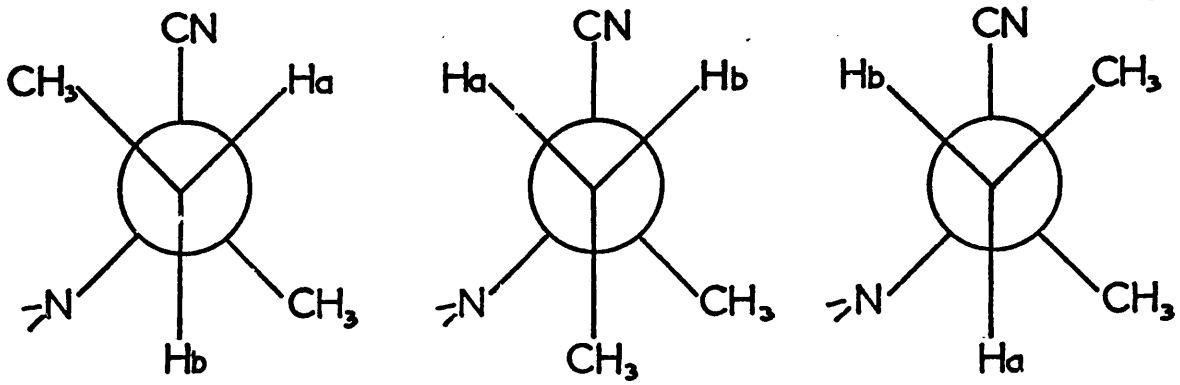
* previously prepared and characterised[49].

In the above series yields were generally good, and with the exception of compounds XXV, XXVI and XXVII no difficulty was experienced in isolating the product. The aminonitriles XXVI and XXVII proved more difficult to obtain in a state sufficiently pure for elemental analysis but sufficient spectroscopic evidence was obtained to confirm their structure. It has been reported[69,70] that the introduction of a cyanide group considerably weakens the basicity of an amine but it is difficult to see how this could affect the formation of an aminonitrile. More likely, the proximity of the second benzene ring sterically hinders the reaction.

The NMR spectra are unambiguous. All clearly show an AA^1XX^1 quartet (δ6.7 - 7.3), attributed to the para disubstituted benzene ring and the singlet of the three methyl(methoxyl) protons at around δ3.8. The chemical shift of the signal due to the -NH proton, where present, varies according to temperature and concentration, usually occurring at approximately δ 1.5. Where a cycloalkyl group is present a broad multiplet is produced at high field, sometimes masking the NH signal.

Because of the lack of symmetry in the molecule, the fine splitting of the signals due to the substituent alkyl groups R, R^1 and R^3 is sometimes complex. As may be expected, where a methylene group is adjacent to a chiral centre, the two protons of such a group are nonequivalent[71]. The origin of the nonequivalence may be seen by examining the possible staggered conformations of this type of molecule.

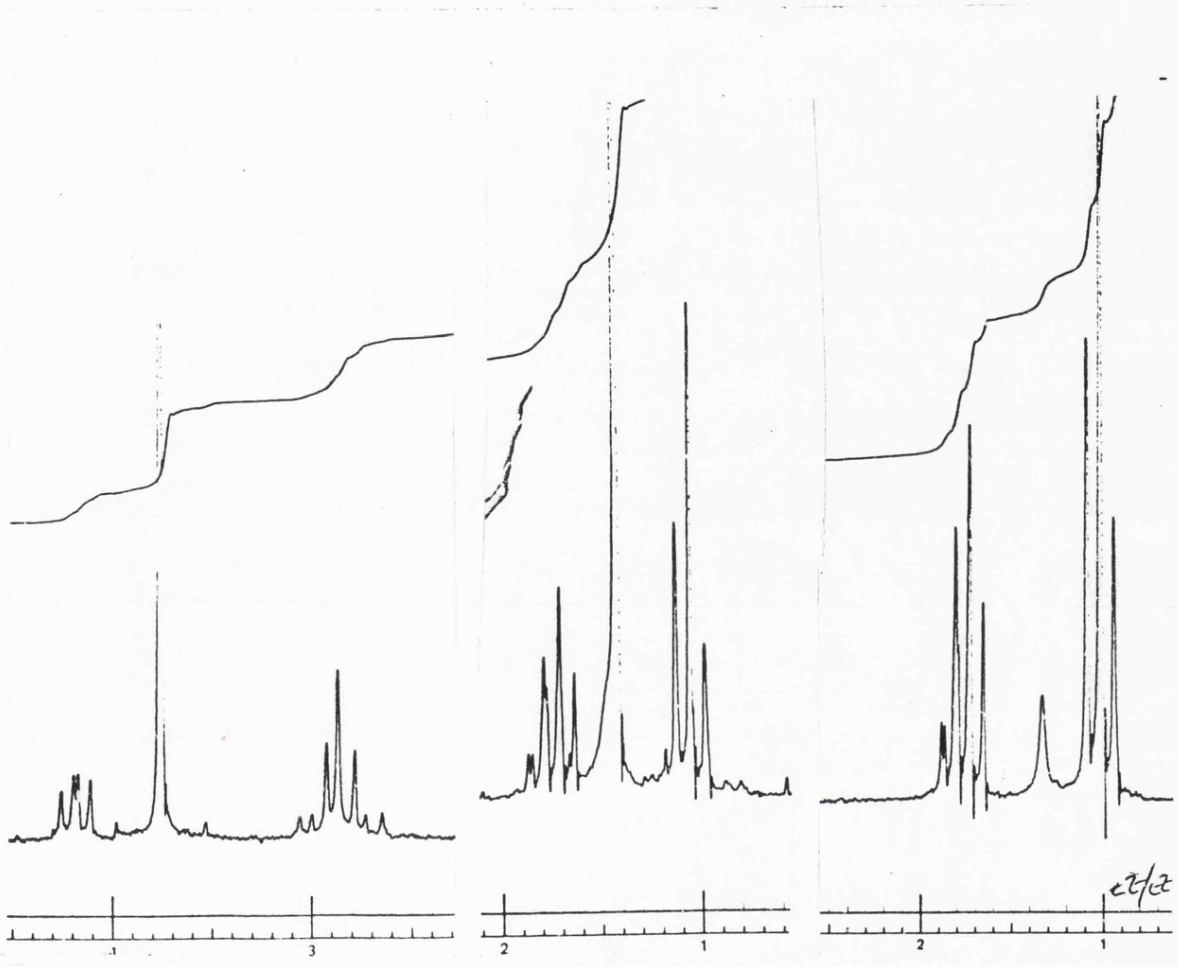
e.g. Compound XVIII



In each conformer the environments of Ha and Hb are different, and furthermore each of the three possible environments of Ha is different from each of those of Hb. Even if all conformers are equally populated Ha and Hb will be neither chemically nor magnetically equivalent.

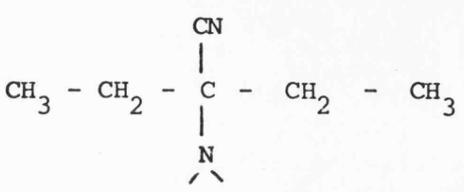
The nonequivalence in most compounds is too small to be observed by NMR spectroscopy but can be clearly seen in the ethyl signal of

compound XVIII and in the coupling between the methine proton and benzylic-CH_2- in compound XXVIII.



XXVIII XVIII XVII

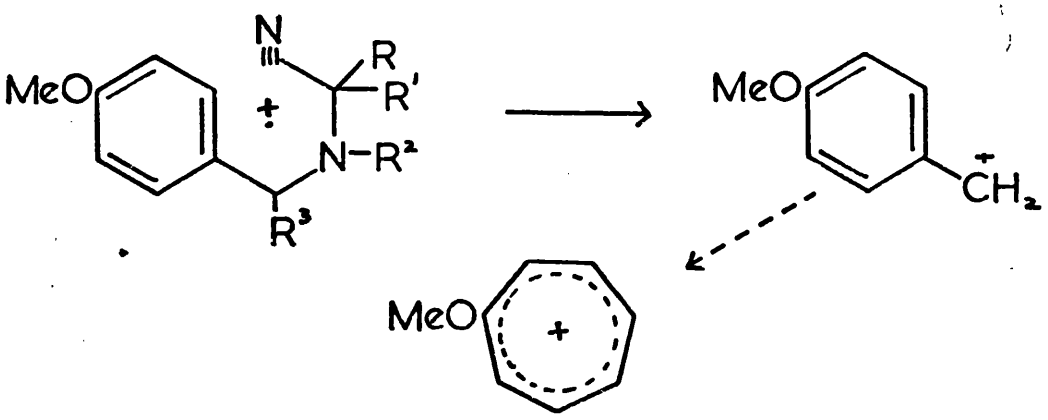
It is interesting that nonequivalence of this kind occurs in compound XVII although the molecule has a plane of symmetry.



In this case reflection in the plane of molecular symmetry interchanges the two methylene groups but does not interchange the two protons within each group[72,73], consequently the two protons in each group are anisochronous.

The C_2 protons of compounds XX and XXI do not show their nonequivalence and resonate at lower field than the protons of the C_2 alkyl groups. This is in accordance with Shoolery's Rules[74,75], the methylene protons of compound XXI appearing as a singlet at 3.54 ppm (calculated value δ 3.50 ppm) and the methine proton of compound XX at δ 3.6 ppm (calculated value δ 3.97 ppm). The agreement between δ calculated and δ observed for the methine signal is better than expected since discrepancies of up to 1 ppm can occur.

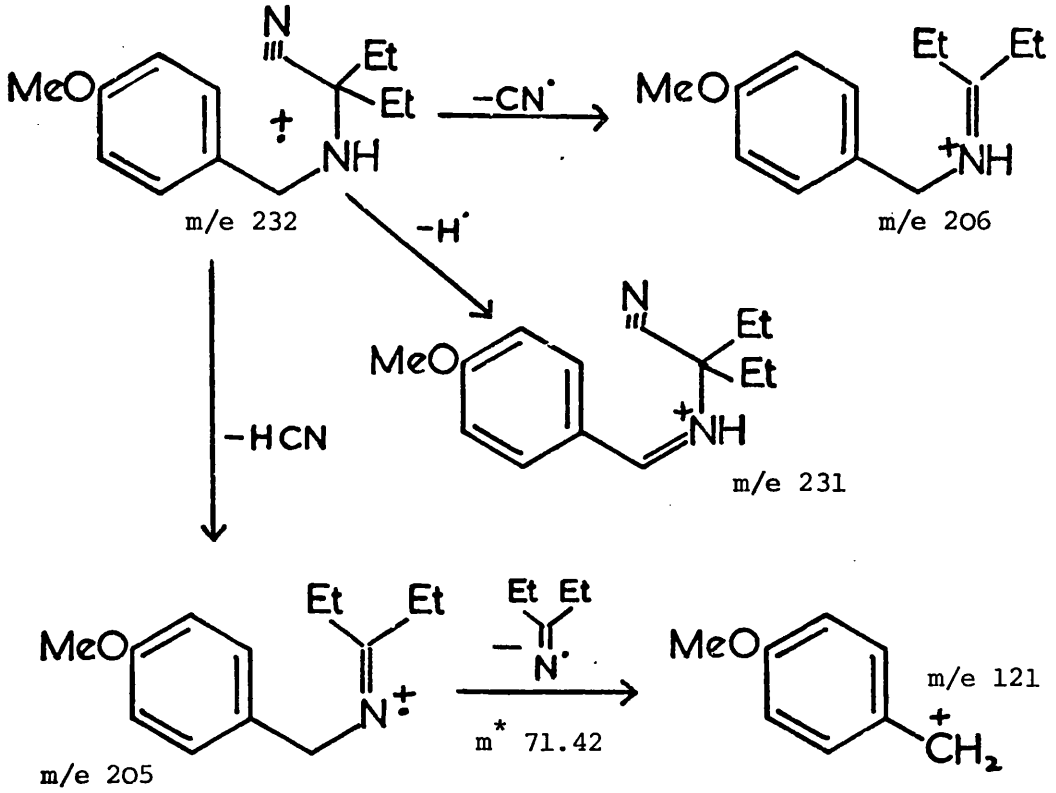
The mass spectra of aminonitriles XVI - XXVIII have been studied. The fragmentation pattern of a series of aliphatic nitriles has been described by McLafferty[76] and further work has been carried out by Rol[77]. In the present work the fragmentation pattern showed little resemblance to that reported, the overriding effect being the stability of the ion at m/e 121 which formed the base peak when present.



The re-arrangement of the p-methoxybenzyl cation to methoxytropylium is in doubt. Basing their argument on appearance potentials Tait[78] and co-workers have shown that the para methoxybenzyl ion exists as such and does not re-arrange to the methoxytropylium ion. However, it is difficult to explain the loss of 26 mass units from this ion unless the re-arrangement has taken place.

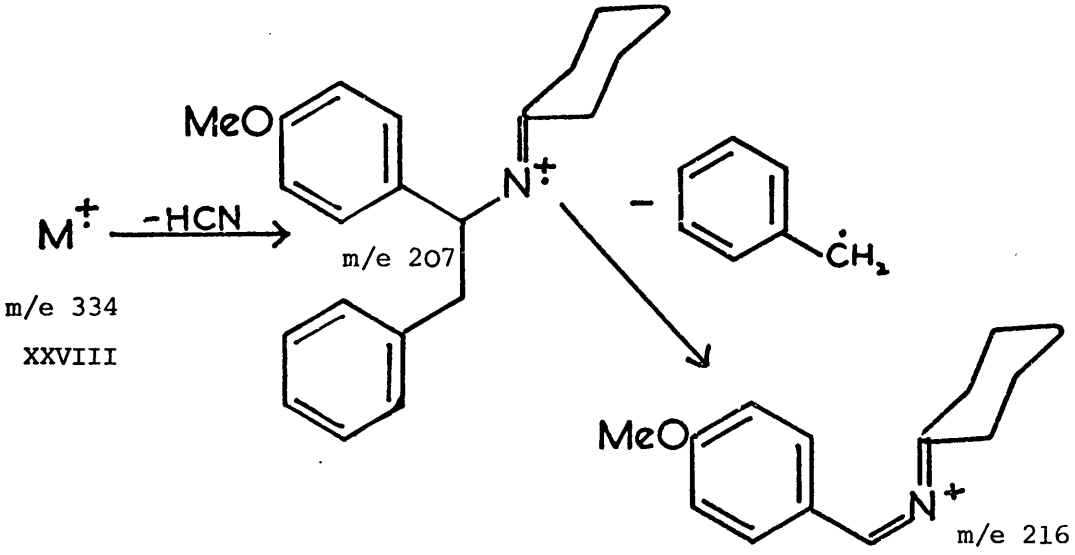
Other common features of fragmentation were the low abundance of molecular ion and the loss of HCN.

A typical fragmentation is shown by compound XVII.

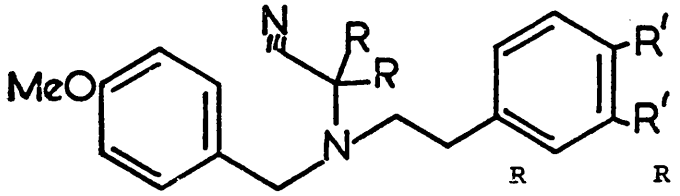


Whilst in the above example, the hydrogen lost in the neutral HCN fragment is postulated as coming from the >NH moiety, this cannot be so when a tertiary nitrogen is present as in compounds XXII - XXVII. In these compounds the most probable source of hydrogen is the benzylic - CH_2.

The only compound in this group where the base peak is not m/e 121 is compound XXVIII. The base peak in this example is m/e 216, formed by loss of HCN and then a benzyl radical from the molecular ion.



GROUP 2 - precursors of N-substituted tetrahydroisoquinolines.

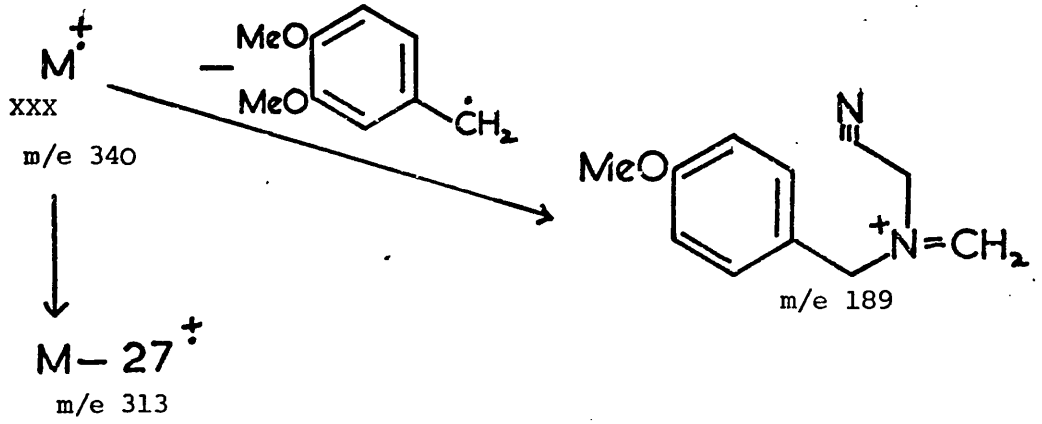


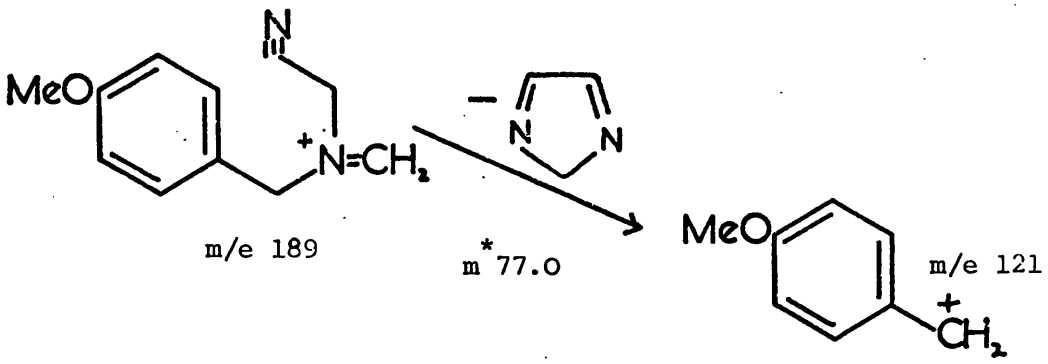
R	R	R^1	R^1	% yield	
H	H	H	H	67%	XXIX
H	H	-OMe	-OMe	63%	XXX
$-(CH_2)_5-$		H	H	48%	XXXI
$-(CH_2)_5-$		-OMe	-OMe	50%	XXXII

The amino nitriles of Group 2 were isolated without difficulty but in variable yield, the presence of the cyclohexyl group possibly causing steric hindrance when present. Elemental analysis and spectroscopic data confirmed their structure.

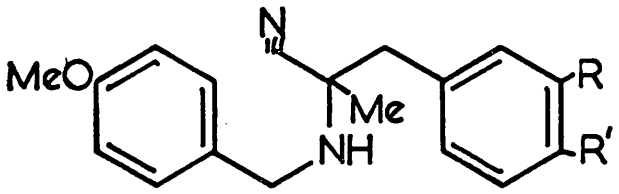
The n.m.r. spectra are less complex than may be expected due to the fortuitous equivalence of the (two) adjacent methylene groups, resulting in a singlet at δ 2.8 ppm.

The mass spectra of compound XXIX and XXX are atypical in the absence (compound XXIX) or very low abundance (compound XXX) of an M.-27 peak indicating loss of HCN from the molecular ion. The preferred fragmentation in these compounds is the loss of a (dimethoxy)benzyl radical producing a daughter ion at m/e 189. Further fragmentation then occurs when the original cyanide moiety is lost as part of a neutral and stable imidazole to give the base peak at m/e 121.





GROUP 3 - precursors of 3-substituted tetrahydroisoquinolines.



R	R^1	% yield	
H	H	80%	XXXIII
-OMe	-OMe	75%	XXXIV
H	Cl	48%	XXXV

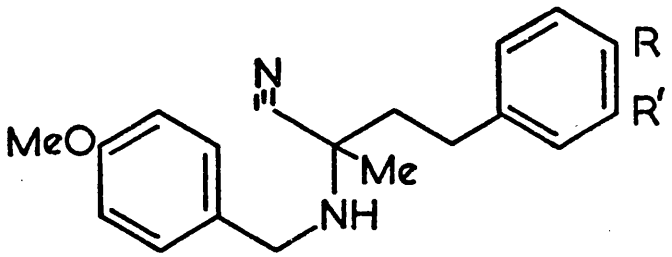
The substituents R and R^1 were chosen in order to deactivate (XXXV) or activate (XXXIV) the ring.

Compound XXXIII was formed in the reaction mixture in crystalline form whilst XXXIV and XXXV were produced as oils. The latter crystallised on standing for several weeks but the compound XXXIV could not be obtained in crystalline form. The hydrochloride of XXXIV was found to be unstable and satisfactory elemental analysis could not be obtained for this compound.

The spectroscopic data was in all cases satisfactory.

The i.r. spectra all showed absorption γ max ca. 2250 cm^{-1} indicating a C ≡ N group and the absence of, or very weak absorption (XXXIV) at γ max ca. 1650 - 1800 cm^{-1}. The n.m.r. spectra were unambiguous, the asymmetric centre at carbon 2 having no visible effect on the splitting. Fragmentation in the mass spectrometer was characteristic of compounds of this type, the molecular ion losing HCN and the base peak being at m/e 121 i.e. the 4-methoxybenzyl ion.

GROUP 4 - precursors of 2-benzazepines.



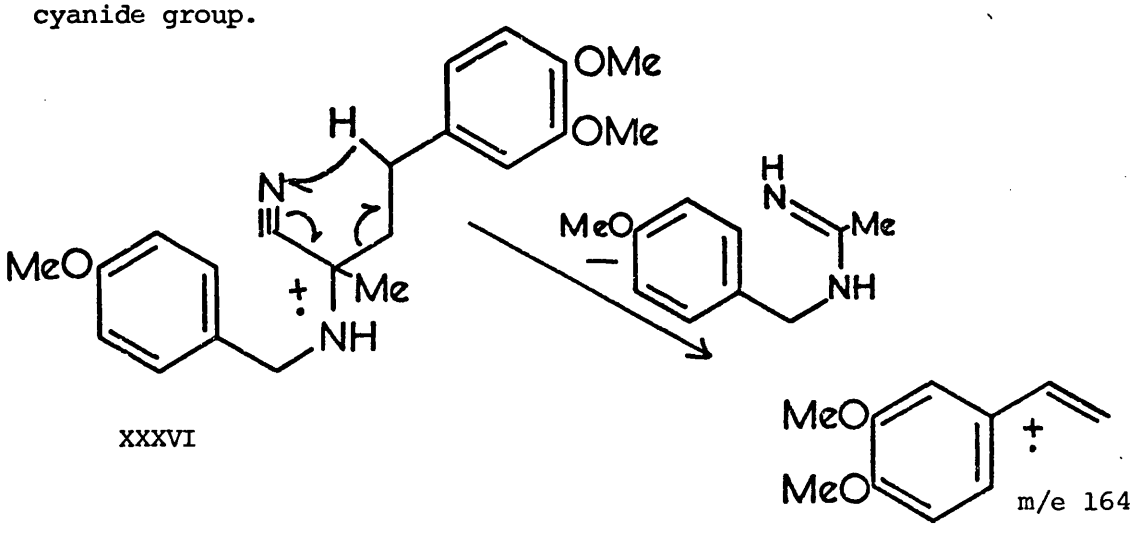
R	R^1	% yield	
OMe	OMe	65%	XXXVI
H	H	65%	XXXVII

The two aminonitriles designed as benzazepine precursors were prepared without difficulty, compound XXXVI as a low melting point solid and compound XXXVII as an oil which fortunately gave a stable hydrochloride.

Infra red spectra showed -CN stretching at 2250 cm^{-1}.

The n.m.r. spectra were made complex by the chirality at C2 causing the two groups of methylene protons of the phenethyl moiety to appear as multiplets, a situation comparable to that seen in compound XVIII.

The mass spectra of both XXXVI and XXXVII show the usual loss of HCN from the molecular ion and have m/e 121 (methoxybenzyl) as the base peak. The methoxyl groups of compound XXXVI appear to affect one fragmentation pathway, giving an ion at m/e 164 (70%) whilst the corresponding ion at m/e 104 is not present in compound XXXVII. This is postulated as a McLafferty type re-arrangement involving the cyanide group.

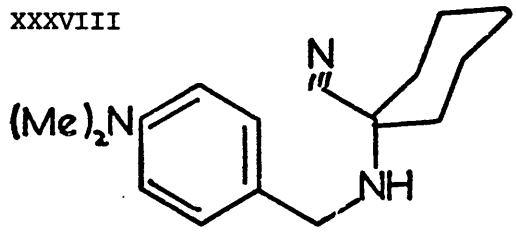


XXXVI

m/e 164

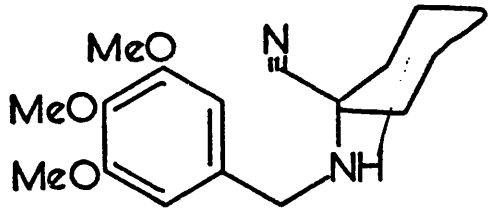
GROUP 5 - other nitriles

Compound XXXVIII



Prepared from 4-dimethylaminobenzylamine with cyclohexanone and HCN compound XXXVIII was obtained in crystalline from and characterised by elemental analysis and unambiguous spectroscopic data.

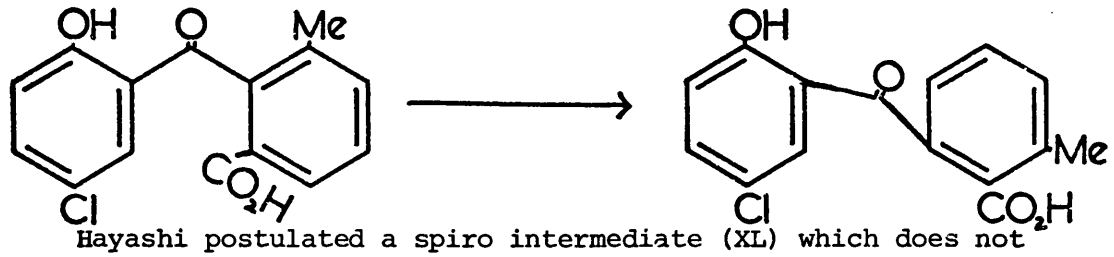
XII.



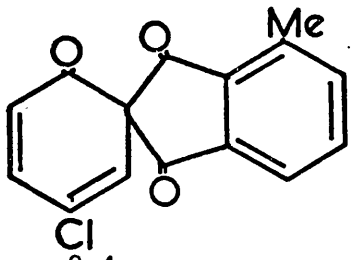
This compound had previously been characterised[49].

Hayashi Re-arrangement

Hayashi[2-6] was the first worker to report the occurrence of a molecular re-arrangement on heating certain substituted o-benzoyl-benzoic acids with concentrated sulphuric acid.



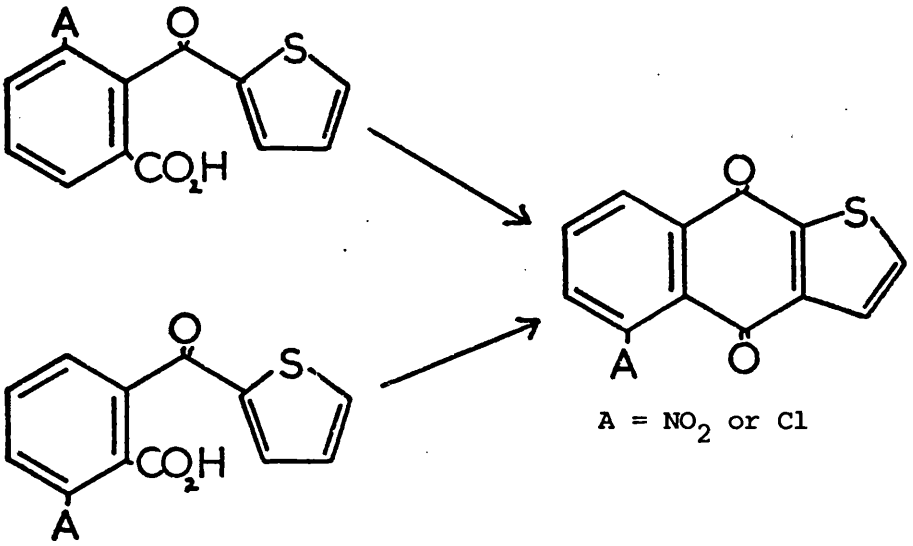
Hayashi postulated a spiro intermediate (XL) which does not carry a charge.



A series of papers[2-4] by the same author described many similar reactions. Due to the limited methods of characterisation available many of the structures assigned by Hayashi were incorrect and a summary of his work together with corrected structures has been published[6].

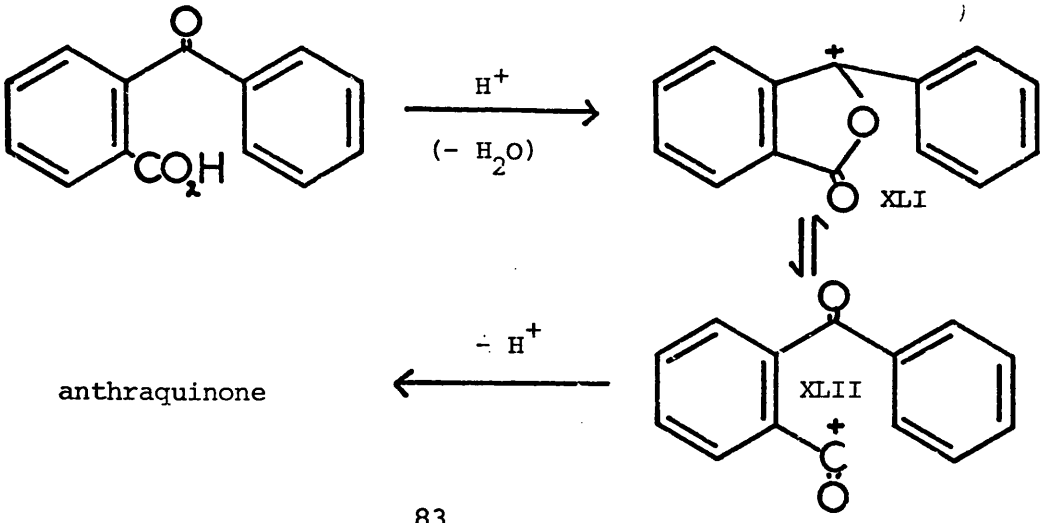
In the preparation of dibenzanthraquinone from 1-(1-naphthoyl)-2-naphthoic acid a comparable re-arrangement was noted by Cook[79]. This worker postulated a hydroxylactone intermediate and severely criticised the mechanism of Hayashi.

Schroeder and Weinmayr[80] claimed that ring closure of the chloro- and nitro- thenoylbenzoic acids proceeded normally when the substituent was meta to the thenoyl group but with re-arrangement when in an ortho or para position. Conversely, amines cyclised normally when ortho or para but re-arranged when meta to the thenoyl group.

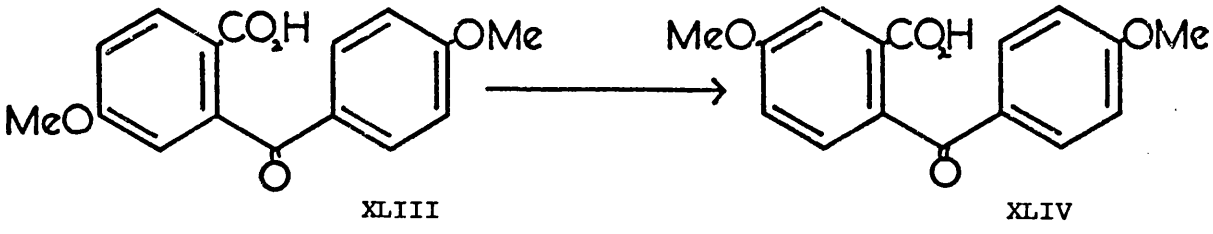


This work was later shown to be in error by Newman and Irhman[81] on grounds of gross impurity in the starting materials.

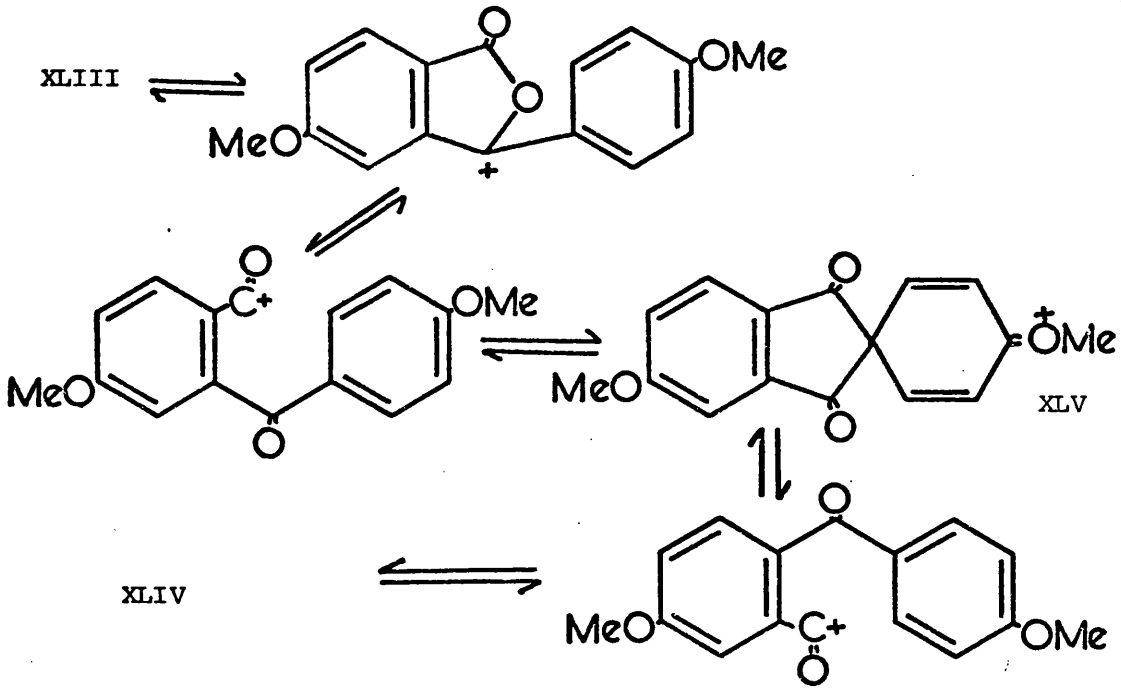
In an attempt to explain the ease of formation of anthraquinone from benzoylbenzoic acid Newman[82] proposed that intramolecular acylation occurs through a cyclic carbonium ion (XLI) which, on heating, cleaves to yield an acyl carbonium ion (XLII).



Sandin and co-workers[83] re-arranged 2-(4-methoxybenzoyl)-4-methoxybenzoic acid (XLIII) to 2-(4-methoxybenzoyl)-5- methoxybenzoic acid(XLIV) by means of concentrated sulphuric acid at 65°.



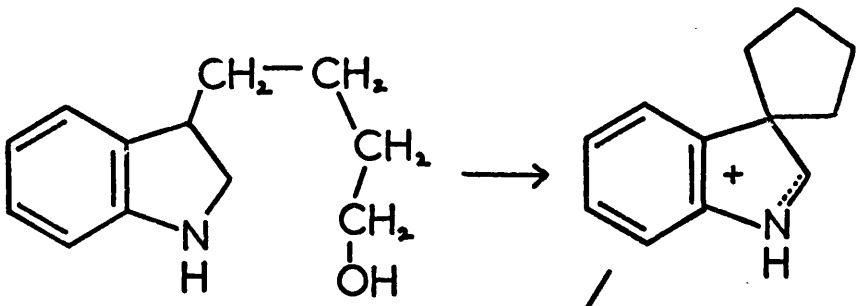
In discussing a possible mechanism for the above reaction these workers accept the formation of the carbonium ions proposed by Newman and further postulate the formation of a "non-classical 'phenonium' cationic type structure" (XLV).



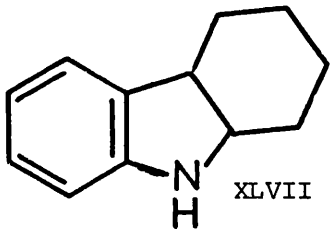
Further evidence for Newman's mechanism is provided by the work of Noyce and Kittle[84,85] in a spectroscopic study of the protonation of benzoylbenzoic acids. Vinnik and co-workers[86] describe the dominant ion as equivalent to XLII, and results obtained by Stevens and Crowder[87] using benzoylbenzoic acid-carboxyl-^{14}C also support this mechanism.

In the preparation of 1,5- and 1,8-dimethylanthraquinones. Cristol and Caspar[88] use the Sandin-Newman mechanisms to explain their results and suggest that the spiro-intermediate postulated by Sandin is the rate determining step in the Hayashi Re-arrangement. These workers also show that temperature plays an important role.

The formation of a cyclic intermediate (nonisolable) is now accepted in many different types of organic reaction[89], and is demonstrated most convincingly when 4-(3-indolyl)-1-butanol (XLVI) containing tritium in the 4 position is cyclised to hexhydrocarbazole (XLVII). Tritium is found in both the 1 and 4 positions[90].

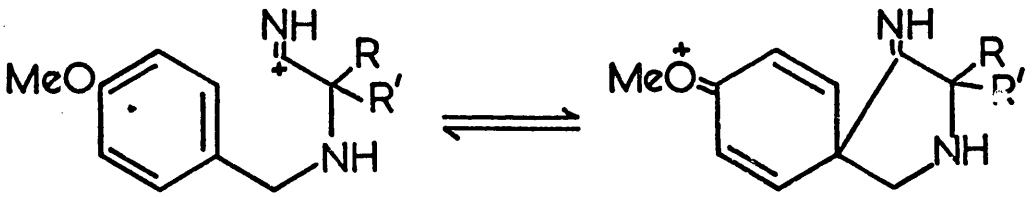


XLVI



XLVII

In the present work a cyclic intermediate is postulated as (XLVIII).



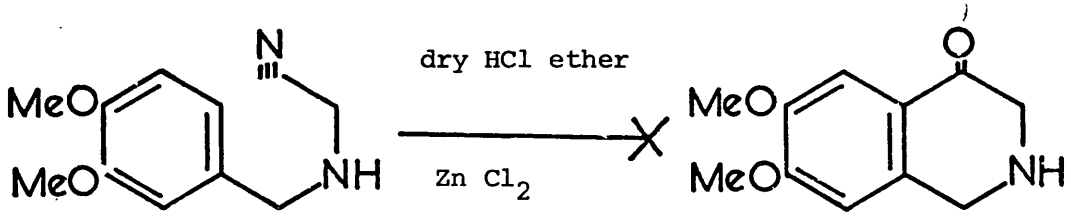
Only one compound (XIL) gave different products at room temperature compared with cyclisation carried out in heated sulphuric acid. To effect cyclisation at room temperature the benzylamino-nitrile was dissolved in concentrated sulphuric acid at 0°C and allowed to stand overnight. The "hot" cyclisations were carried out at 50°C for four hours. Other workers have used much higher temperatures for a shorter period of time e.g. 170° for 3 minutes[81].

The Hayashi Re-arrangement, (and hence the cyclisation) has been reported as being "independent of the condensing agent"[80].

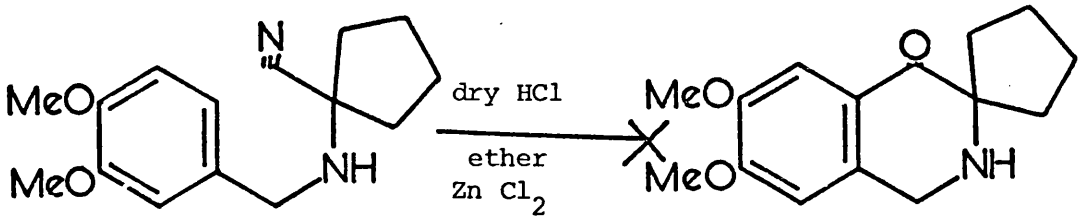
This is not in agreement with the cyclisation of benzylaminonitriles. Aluminium chloride, polyphosphoric acid and hydrochloric acid under a variety of conditions all led to failure [1(b)], only concentrated sulphuric acid giving cyclised products.

CYCLISATION OF AMINONITRILES

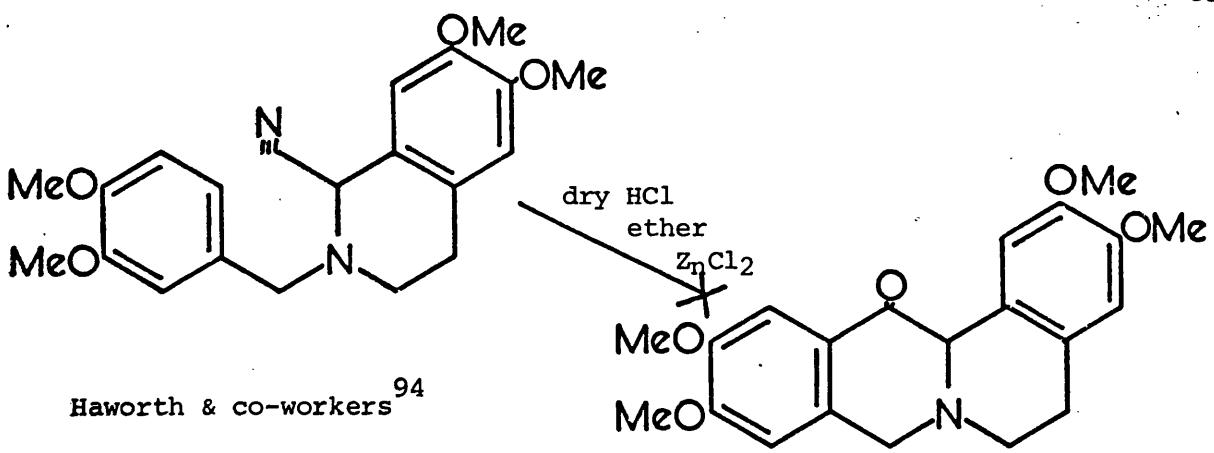
Such cyclisations as give 4-keto-tetrahydroisoquinolines might be regarded as intramolecular Hoesch reactions[91], offering a very obvious route to such compounds. There has been at least four previous attempts at similar reactions[92,93,94], only one of which was successful[1]. Dey and Govindachari[92], formally reported failure, with the object of demonstrating, in conjunction with other unsuccessful reactions, the difficulty of isoquinoline synthesis from simple benzylamines. The other unsuccessful attempts were published amongst other work. The originators of the unsuccessful work were apparently unaware of each others experiments, since they all used the same reaction conditions, their choice of reagents apparently being governed by the classical Hoesch procedure.



Dey & Govindachari[92]



Oakeshott & Plant[93]

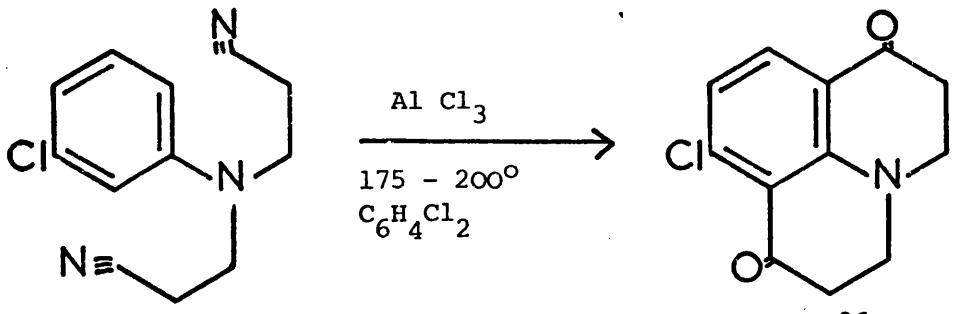


Haworth & co-workers[94]

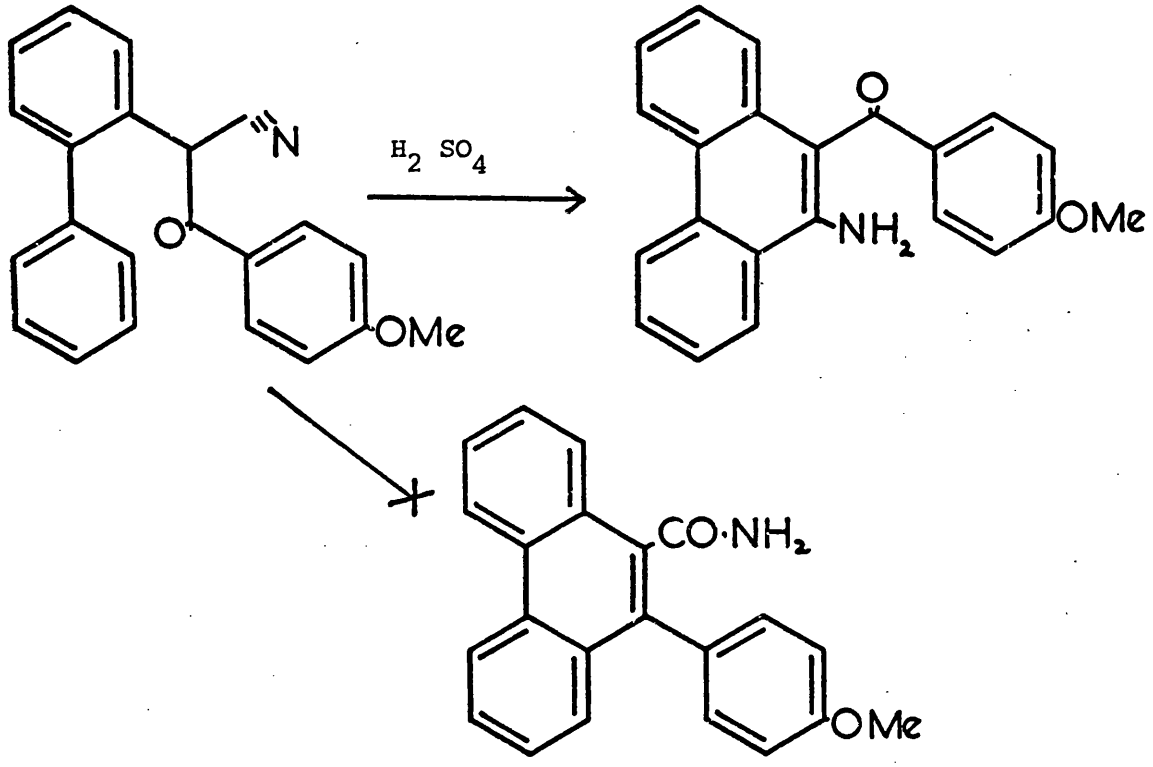
Oakeshott and Plant[93] also report failure when cyclisation was attempted in concentrated sulphuric acid. This is the basis of the present work and no explanation can be offered for such an unfortunate result.

The other failures are probably due to the insolubility of the aminonitrile hydrochloride in dry ether. Using classical Hoesch conditions the aminonitrile hydrochloride would precipitate out immediately and any reaction would then have to proceed heterogeneously.

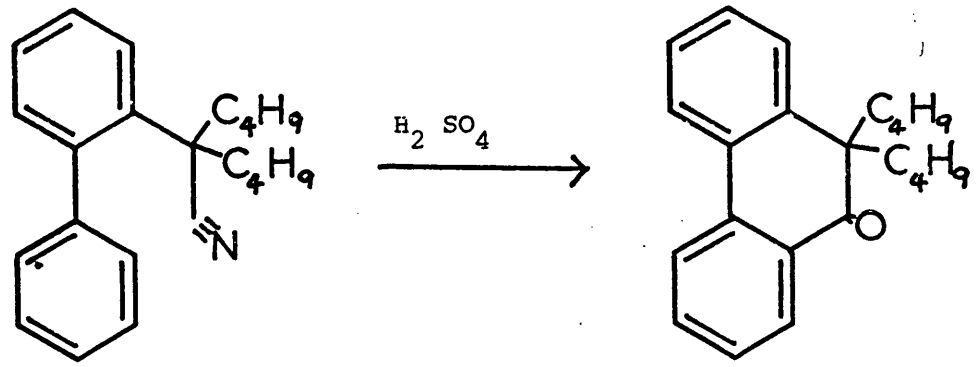
However, an analogous reaction[95] gave a quinoline, even with a deactivating group in the ring, using a high temperature and an aluminium chloride catalyst.



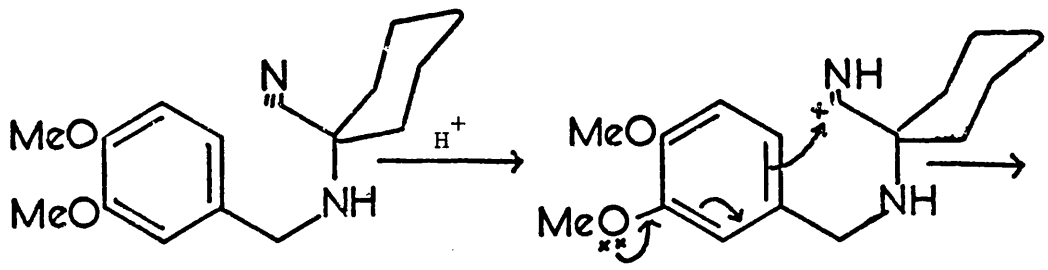
Of greater significance was the work of Bradsher[96] and co-workers who obtained a phenanthrylamine from a nitrile cyclisation using cold concentrated sulphuric acid. It is interesting to note that whilst an alternative cyclisation involving the ketone group was possible, the nitrile cyclisation was preferred.

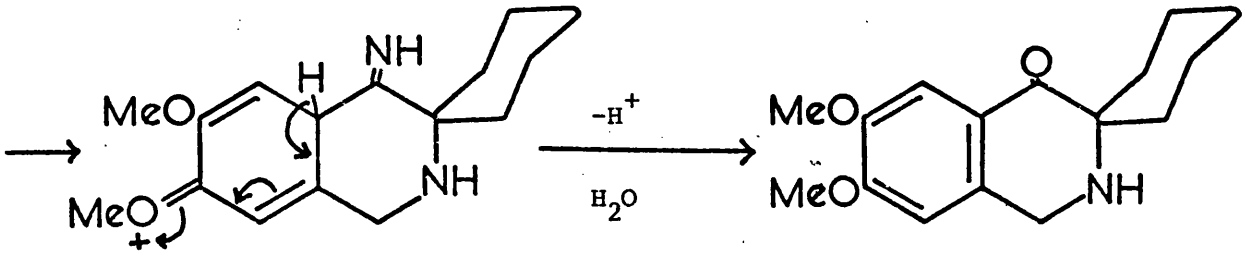


Excellent results were obtained when this reaction was applied to simple derivatives.



This approach was successfully followed by Harcourt and Waigh[1] who showed that benzylaminonitriles could be cyclised to 4-keto-tetrahydroisoquinolines in good yield providing the aromatic ring was activated. The absence of an activating group led only to the amide. The following mechanism was postulated.



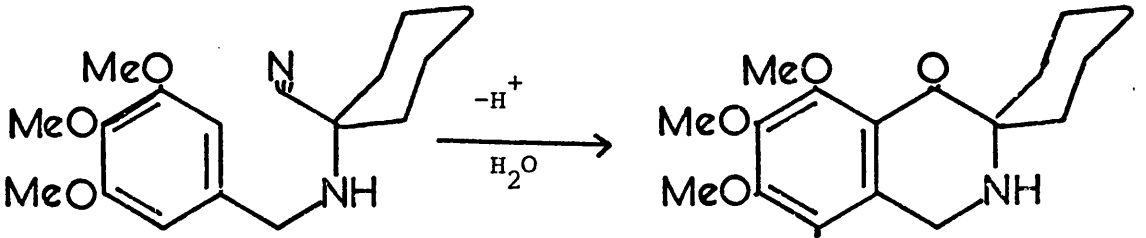


The present work does not exclude the above mechanism but shows that an alternative and overriding pathway may be followed. This is exemplified by the cylisation of 2-(3,4,5-trimethoxybenzylamino)-2-spirocyclohexylacetonitrile (XIL).

1/ in cold concentrated sulphuric acid overnight

2/ in concentrated sulphuric acid at 50°C for 4 hours.

1) The cold cyclisation gave a 4-keto-tetrahydroisoquinoline in 22% yield together with 7% of the amide formed by hydration. The two compounds were separated by fractional crystallisation and characterised by elemental analysis and spectroscopy. The important feature being the chemical shift of the one aromatic proton of the ketone at δ 6.38 ppm.



XIL XLIX

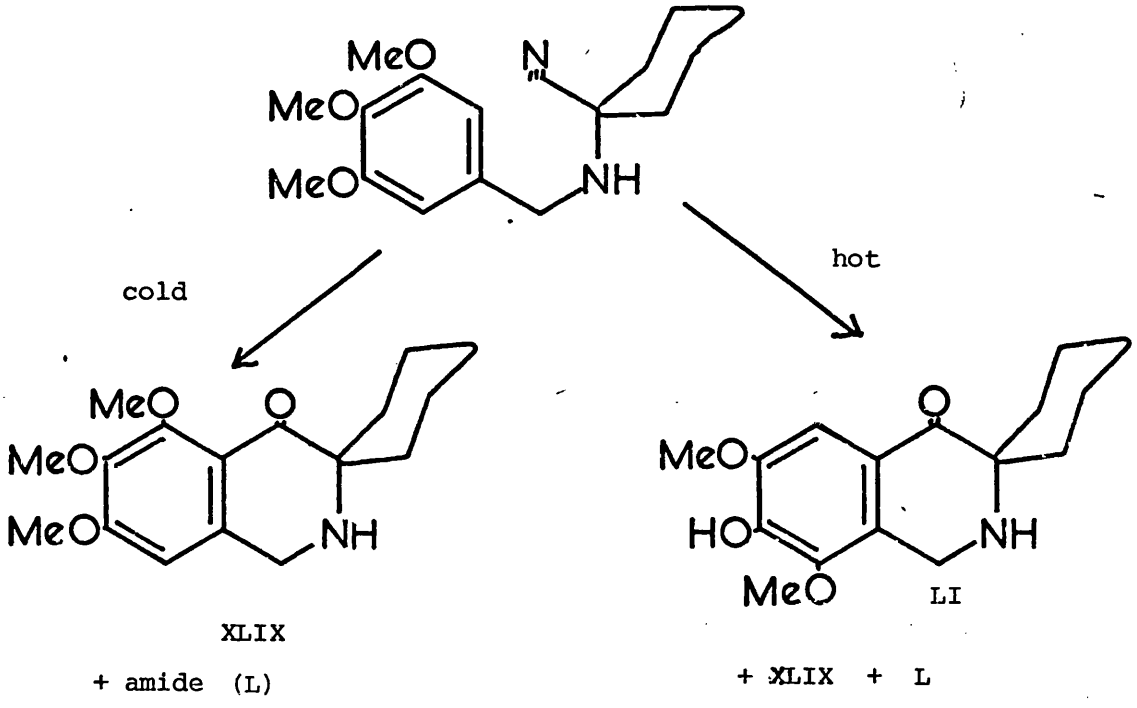
Such a product is entirely in keeping with the postulated mechanism of Harcourt and Waigh[1].

2) The "hot cyclisation" gave, after basification with 5N sodium hydroxide and chloroform extraction the same two compounds (XLIX and L) but in low yield, less than 7% of each. Both compounds were characterised by spectroscopy and by mixed melting point with the products of cold cyclisation. Re-acidification of the extracted

aqueous solution with concentrated hydrochloric acid gave a copious white precipitate (1.4 g) which was filtered off, washed and suspended in distilled water. Basification with sodium bicarbonate, extraction and recrystallisation from petroleum ether gave 1.0 g (70%) of a 4-keto-tetrahydroisoquinoline (mp.149°), the n.m.r. spectrum of which showed a single aromatic proton at δ 7.34 ppm. Spectroscopy and elemental analysis also showed that cyclisation had occurred together with concomitant O-demethylation, thus explaining the solubility in strong alkali.

The shift of the aromatic proton signal to lower field is explained by assigning this proton to the C-5 position, there being deshielded by the carbonyl group.

The results of the two cyclisations are summarised:-

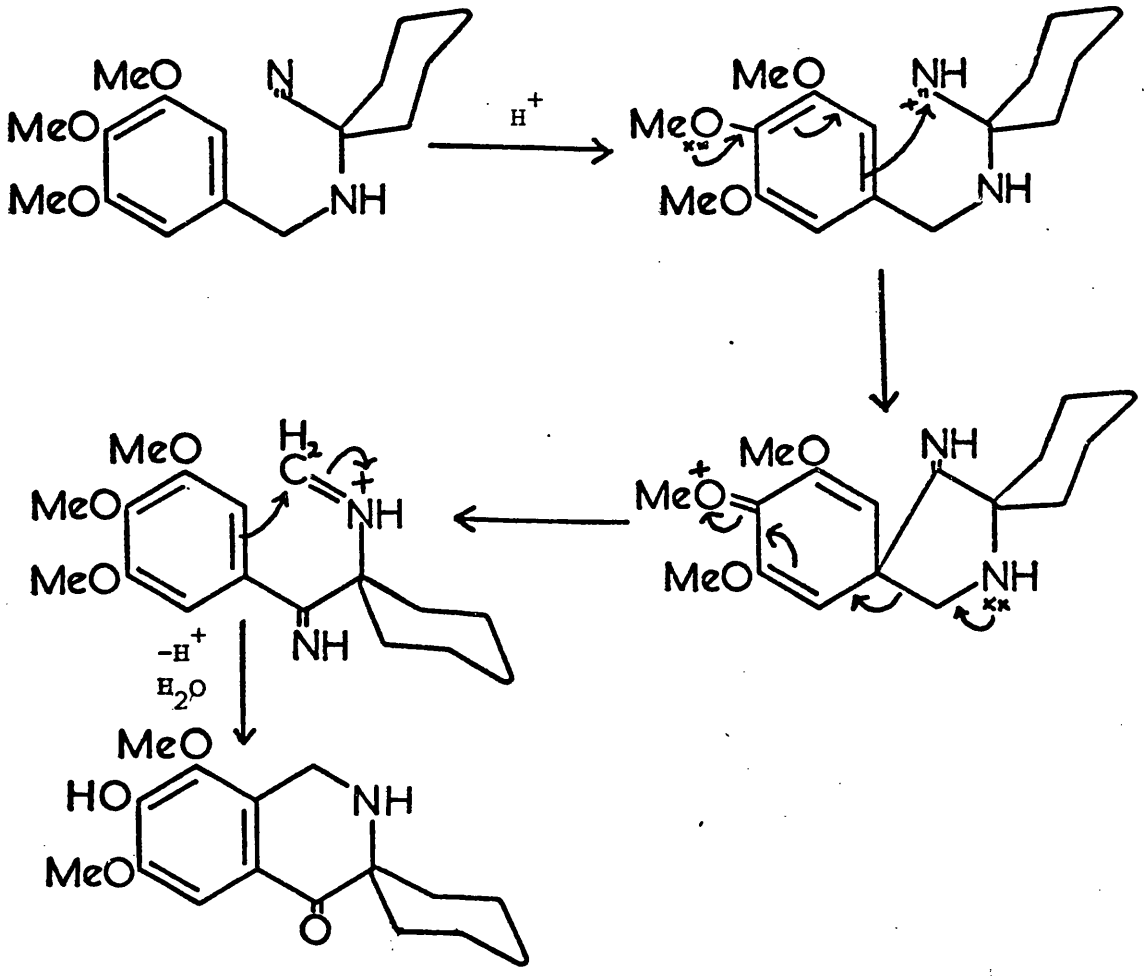


XLIX

+ amide (L)

+ XLIX + L

The formation of Ll cannot be explained by the aforementioned classicial cyclisation and a mechanism reminiscent of the Hayashi rearrangement is postulated.



That O-demthylation occurs is clearly shown by spectroscopy, the n.m.r. spectrum giving a "deuterable" peak at δ 4.10 ppm, the mass spectrum showing a molecular ion at m/e 291 and the infra-red spectrum giving a sharp peak at ca.3600 cm^{-1}. This is not in accord with the work of Grethe and his co-workers[97], but may occur in the transition state giving electronic stability and relieving steric strain. Such a "central" methyl group is comparatively easily lost under acidic conditions[98] but this has not been proven for L1.

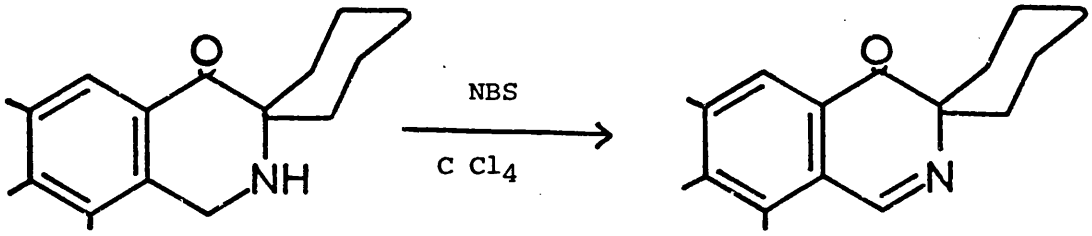
Experiments to determine the position of the hydroxyl group relative to the two remaining methoxyls were unsuccessful.

A sample of L1 was examined by nuclear magnetic resonance after addition of euroshift F[99], which, it was hoped, would complex with the various lone pair sites on the molecule and induce downfield shifts of adjacent protons. Unfortunately this compound proved

incompatible with the reagent, probably due to the acidic nature of the phenolic hydroxyl group and no usable information was obtained.

A detailed examination of the methoxy signals showed two peaks resonating at 350.2 Hz and 352.5 Hz. The signals were then irradiated in turn to detect any long range coupling. Irradiation of each methoxyl group produced a slight enhancement of the aromatic signal whilst irradiation of the aromatic proton enhanced the downfield methoxy signal. The latter effect is not in itself a criterion for decoupling as it could be a consequence of a nuclear Overhauser effect[100] which depends on the proximity of protons and <u>not</u> on spin-spin coupling.

Integration showed that there was indeed an nOe enhancement. Irradiation of the methoxyl signal at 352.5 Hz whilst monitoring the aromatic proton gave increase of 19.4%. No enhancement was obtained when the high field methoxyl signal was irradiated and the $-CH_2-N<$ signal was monitored. This was not unexpected due to the distance involved between the two groups and the fact that the benzylic $-CH_2$ is not part of a rigid structure. To increase the rigidity of the structure an unsuccessful attempt was made to oxidise L1 tc the 3,4-dihydro compound L11 using N-bromosuccinimide in carbon tetrachloride.

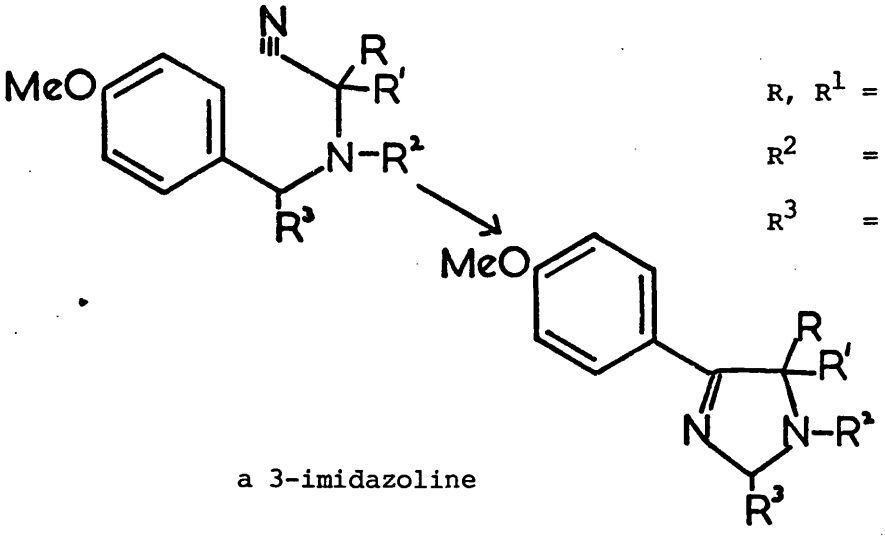


LI LII

An attempt to remove the phenolic hydroxy group by the method of Lonsky and co-workers[101] was also unsuccessful, possibly because of steric hindrance by the two remaining methoxyls.

Unequivocal confirmation of the structure could not be obtained with the material available but the suggested structure is in accord with the work of Bogert and Ehrlich[102] who prepared 4-hydroxy-3, 5-dimethoxybenzoic acid by heating 3,4,5-trimethoxybenzoic acid in fuming sulphuric acid at 40° for 30 minutes. This work was repeated by Alimchandani and Meldrum[103] who confirmed the structure of the demethylated product by oxidation to 2,6-dimethoxy-p-benzoquinone.

Cyclisation of Group 1 nitriles



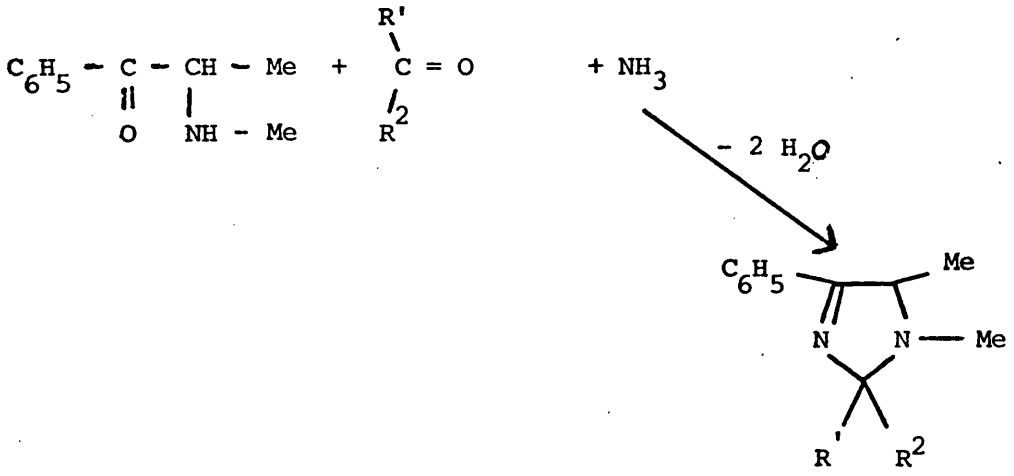
R, R^1 = alkyl

R^2 = H or Me

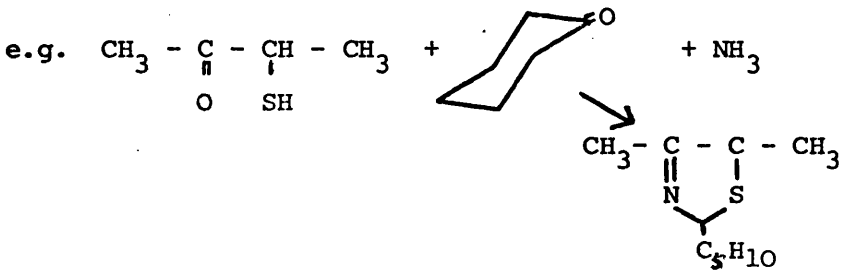
R^3 = H or benzyl

a 3-imidazoline

The 3-imidazolines were first reported by Kirchner[104] as recently as 1959. Kirchner reacted salts of α-amino or α-alkylaminoketones with carbonyl compounds and ammonia to produce a series of substituted 3-imidazolines.

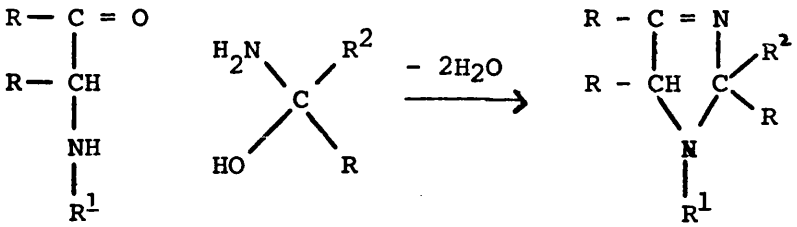


This publication was stimulated by the work of Asinger and Thiel[105] who had earlier reported the synthesis of 3-thiazolidines by an analagous reaction.

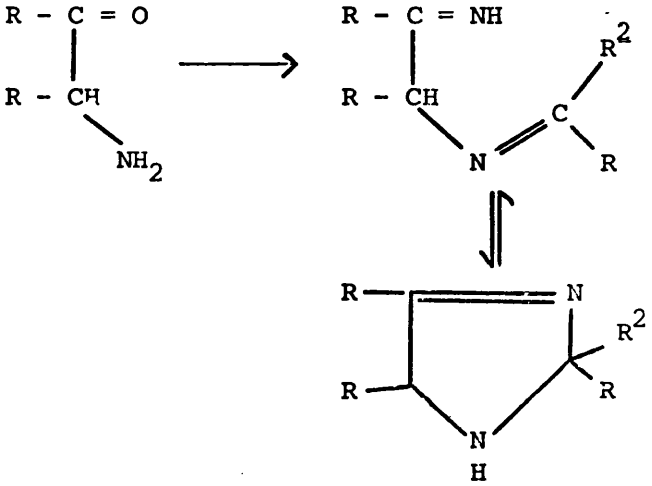


Three alternative mechanisms are postulated by Kirchner.

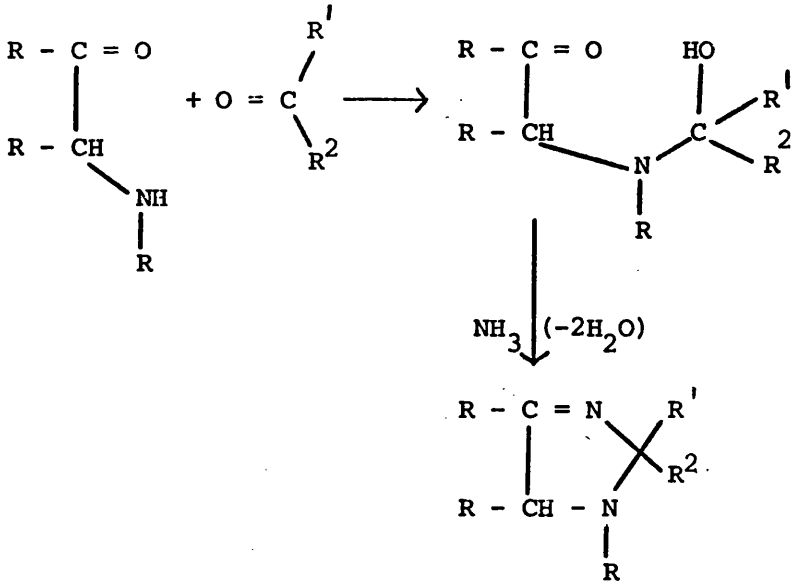
Mechanism 1.



Mechanism 2.

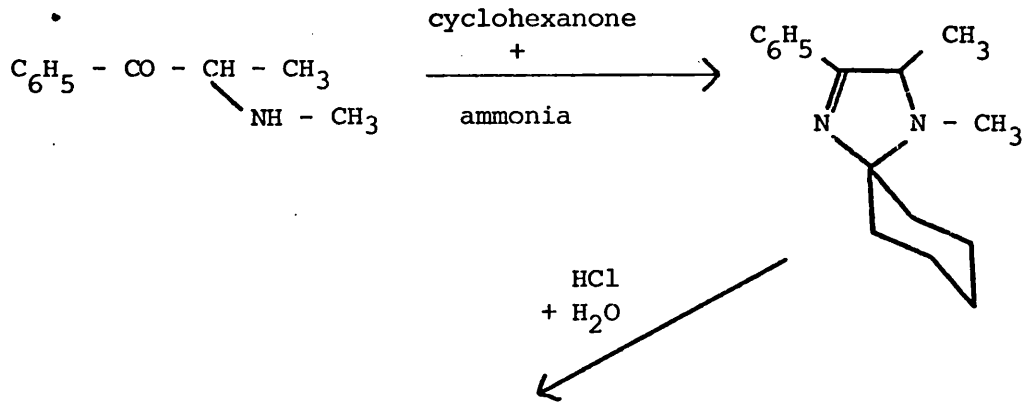


Mechanism 3.



Kirchner makes no claim that these are more than possibilities and indeed all are open to criticism in the absence of further evidence. However a mechanistic pathway comparable to "Mechanism 2" has been postulated for the formation of oxazolidines[106].

Further work by Kirchner[107] attempts to explain the instability of 5-monosubstituted 3-imidazolines. The 3-imidazoline prepared from ∝-(methylamino)-propiophenone gave on hydrolysis of the hydrochloride, ∝-amino-∝phenylacetone.



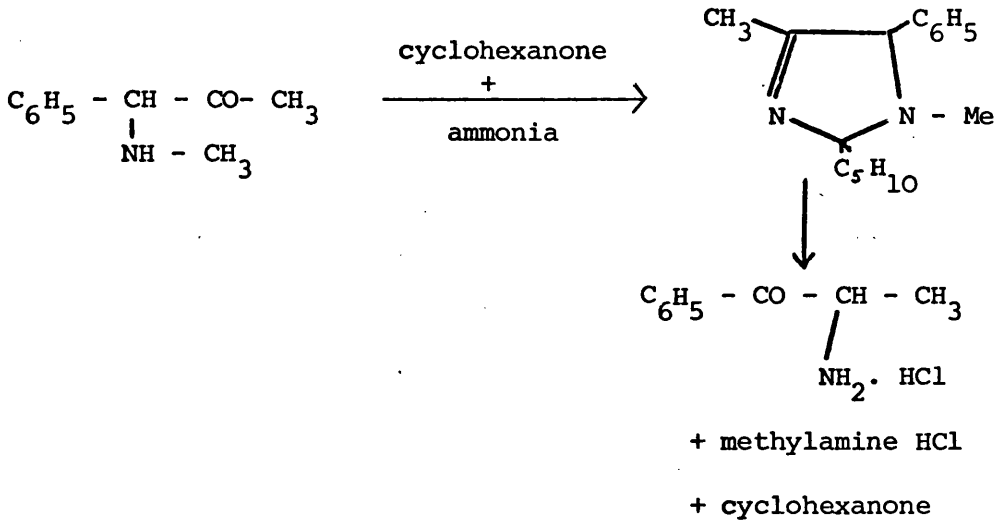
$C_6H_5 - CO - CH(NH - CH_3) - CH_3$ —(cyclohexanone + ammonia)→ imidazoline —(HCl + H_2O)→

$C_6H_5 - CH(NH_2.HCl) - CO - CH_3$

+ methylamine HCl

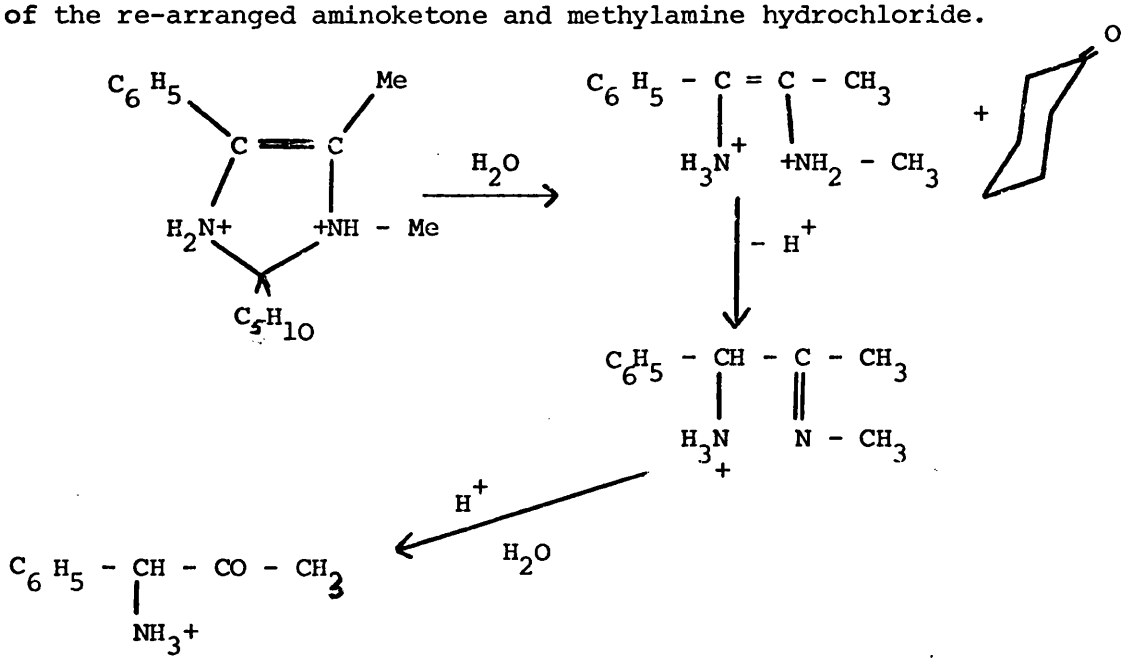
+ cyclohexanone

Conversely, the 3-imidazoline prepared from α-methylamino - α - phenylacetone gave α -~~aminoproprophenone~~ aminopropiophenone after the same sequence of reactions.



This degradation became the subject of a German patent for the preparation of α-aminophenylacetone[108].

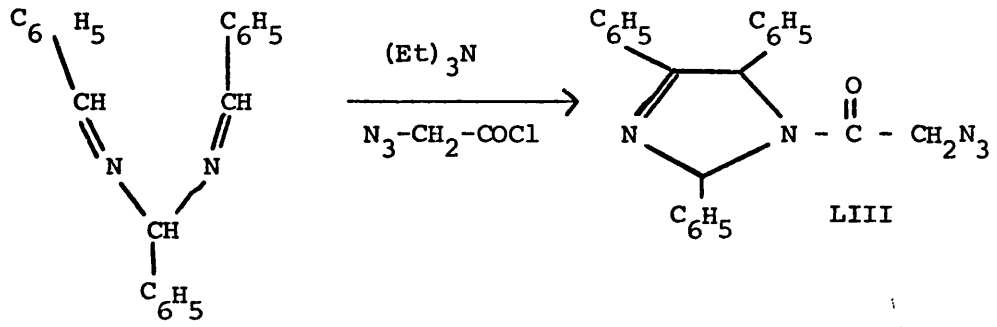
It was postulated by Kirchner that the HCl caused isomerisation of the 3-imidazoline to a 4-imidazoline. The dihydrochloride of the latter is then hydrolysed to regenerate the carboxyl component together with an en-diamine di-hydrochloride which loses HCl and isomerises to a Schiff base. This is then hydrolysed to the salt of the re-arranged aminoketone and methylamine hydrochloride.



Schulz and co-workers[109] showed that 5,5-disubstituted 3-imidazolines gave stable hydrochlorides, thus supporting the earlier work.

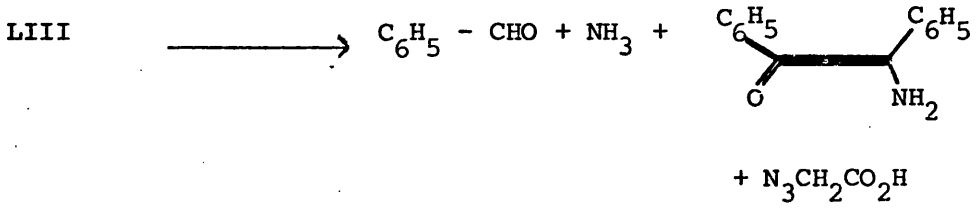
It is unfortunate that neither Kirchner nor Schulz and his co-workers offered any spectral evidence for their findings, all results being based on physical constants and elemental analysis.

A more recent publication[110] reports the formation of a 3-imidazoline LIII by the reaction of hydrobenzamide and azido-acetylchloride in the present of triethylamine.

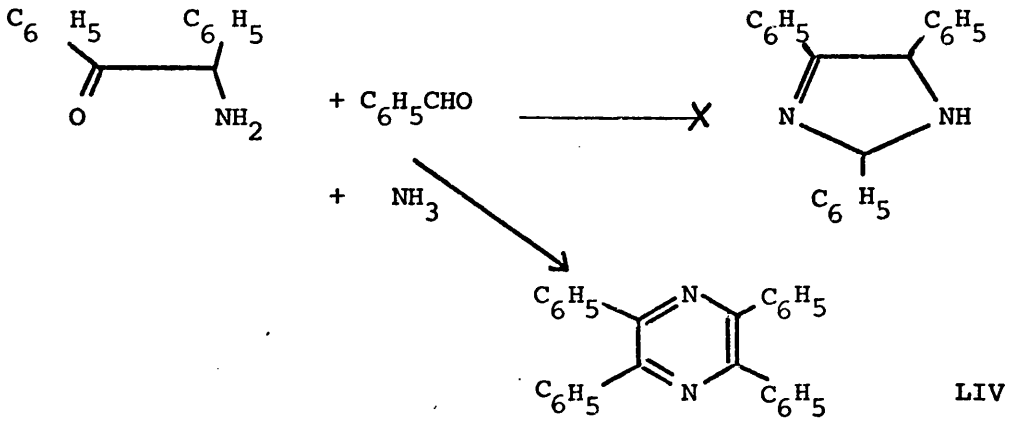


LIII

Hydrolysis of this compound LIII is in accord with the earlier work, producing a carbonyl compound, a base (ammonia) and an amino ketone.



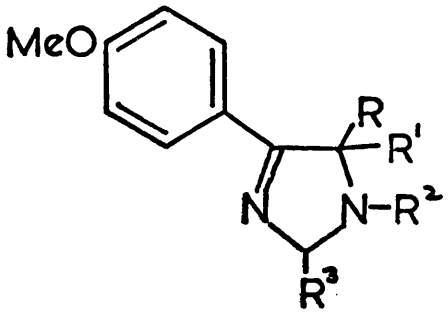
An attempt by these workers to synthesise 2,4,5-triphenyl-3-imidazoline resulted in failure, giving instead the 2,3,5,6-tetraphenylpyrazine LIV.



LIV

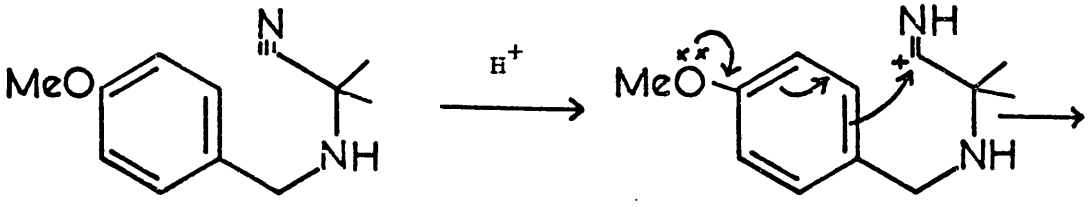
This latter reaction is of interest in the present work and will be referred to later.

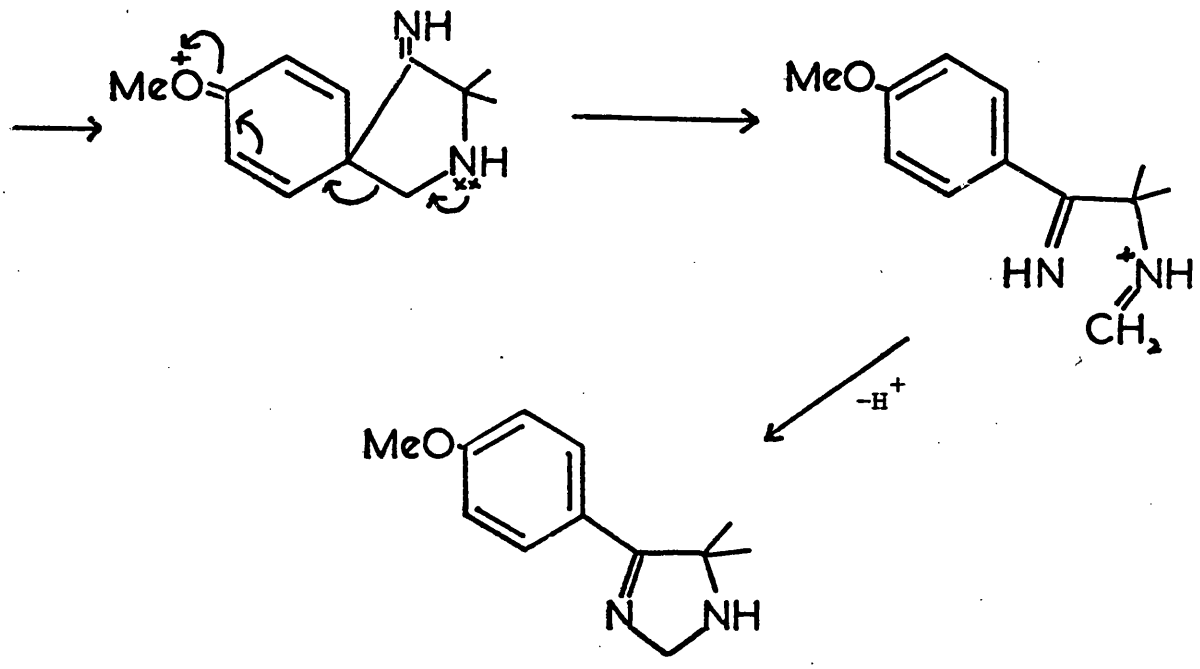
In the present work a series of 3-imidazolines has been prepared:



nitrile	⟶	3-imidazoline				
	R	R^1	R^2	R^3	% yield	
XVI	$-(CH_2)_4-$		H	H	64	LV
XVII	Et	Et	H	H	80	LVI
XVIII	Et	Me	H	H	87	LVII
XIX	Me	Me	H	H	47	LVIII
XXII	$-(CH_2)_5-$		Me	H	96	LIX
XXIII	$-(CH_2)_4-$		Me	H	92	LX
XXIV	Me	Me	Me	H	10	LXI
XXV	$-(CH_2)_5-$		$C_6H_5CH_2-$	H	64	LXII
XXVII	$-(CH_2)_5-$		p-Cl.$C_6H_5CH_2-$	H	10	LXIII
XXVIII	$-(CH_2)_5-$		H	$C_6H_5CH_2$	70	LXIV

The mechanism proposed follows the same pathway as that described for the cyclisation of the trimethoxy nitrile(XIL).





Dreiding molecular models suggest that there is considerable strain involved in forming such a five membered ring. It is therefore assumed that only the low order of reactivity of the aromatic nucleus in the ortho positions (relative to the imine) and the absence of any alternative nucleophile together with the high reactivity of the iminium ion allow the formation of such a ring. A substituted azmethine would appear to have a lower order of reactivity, such compounds giving lower yield and, in the example where the substituent was a veratyl group (XXVI), no identifiable product.

Cyclisation was accomplished by solution of the nitrile in concentrated sulphuric acid, followed by dilution with ice, basification and purification of the product. Whether or not the reaction was carried out at room temperature overnight or at 40° for four hours made no difference to the product or to the yield. The yield was generally good with few exceptions. The trimethyl compound (LXI) showed an unexpected instability in the crude state and the 4-chlorbenzyl compound LXIII was not obtained in sufficiently pure form for elemental analysis.

The spectroscopic evidence for the structures assigned is unequivocal.

The infra-red spectra showed strong absorption at ν max 1600 cm^{-1} indicative of the conjugated -C=N bond, and a weak $>$NH (when present) at ν max 3300 cm^{-1}.

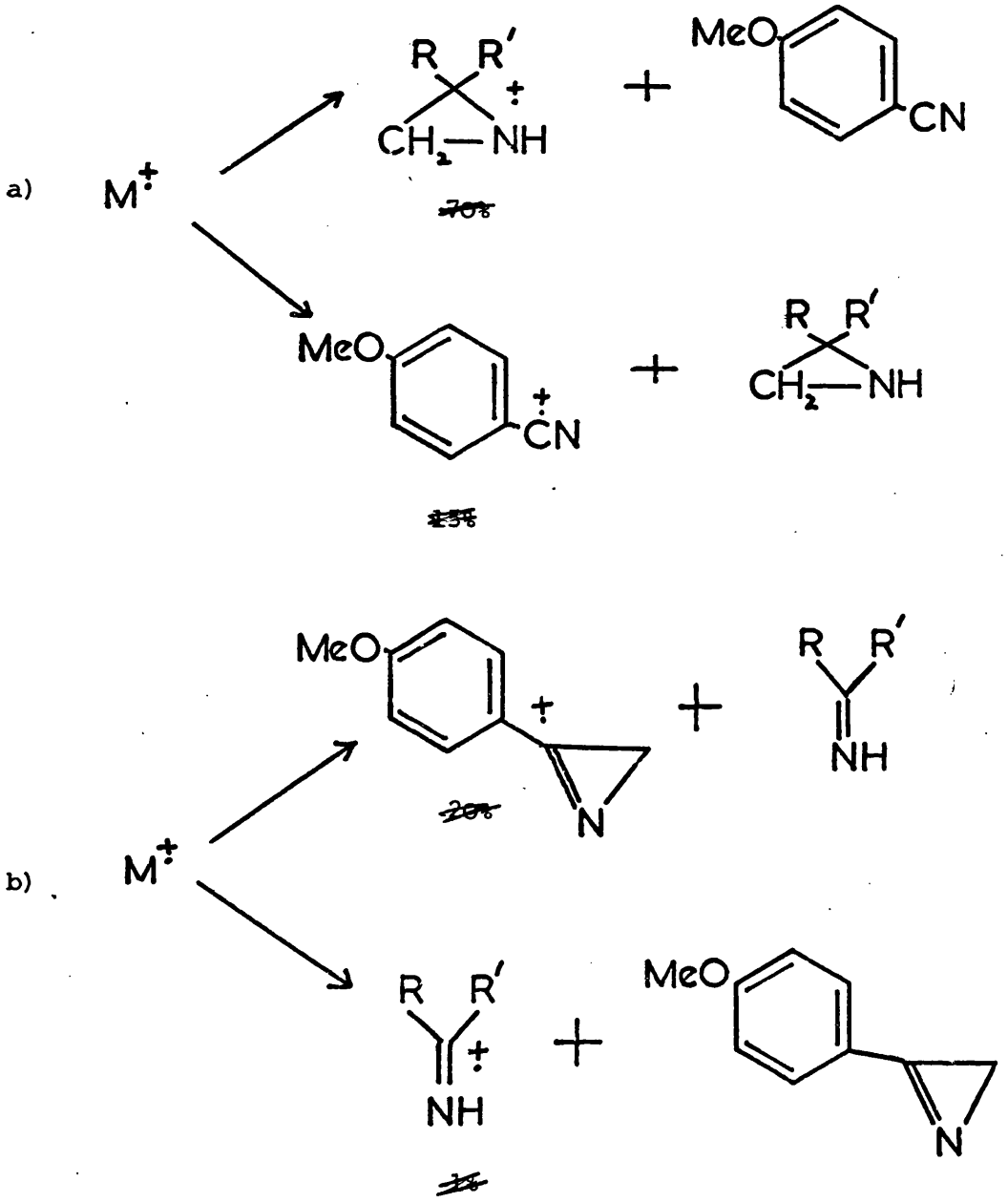
N.m.r. spectra were sometimes complex, caused by molecular asymmetry, but were unambiguous. The AA^1XX^1 pattern of the para disubstituted ring was clearly shown as two doublets at low field, the C_2 protons at δ 4.8 ppm and the methoxyl protons at δ 3.9 ppm. The signals observed from the C5 alkyl protons are of interest from the point of view of asymmetry in the molecule. The nature of the methylene signals of the C5 substituents follows the same pattern as described for their precursors, the most complex being the 5,5-diethyl imidazoline(LVI). N.m.r. spectra run at various temperatures between -40° and 60° failed to produce a simple quartet, thus eliminating the possibility that ring vibrations caused the splitting. The explanation must therefore lie in the non-equivalence of the methylene protons as explained for compounds XVII, XVIII, XXVIII.

In contrast, the C_2 methine proton of compound LXIV shows no effect of chirality, the signal appearing as a triplet at δ 5.2 ppm and the adjacent benzylic $-CH_2$ as a doublet at δ 3.1 ppm. The protons of the benzylic $-CH_2$ are therefore fortuitously equivalent in the cyclised product although they were not so in the corresponding nitrile.

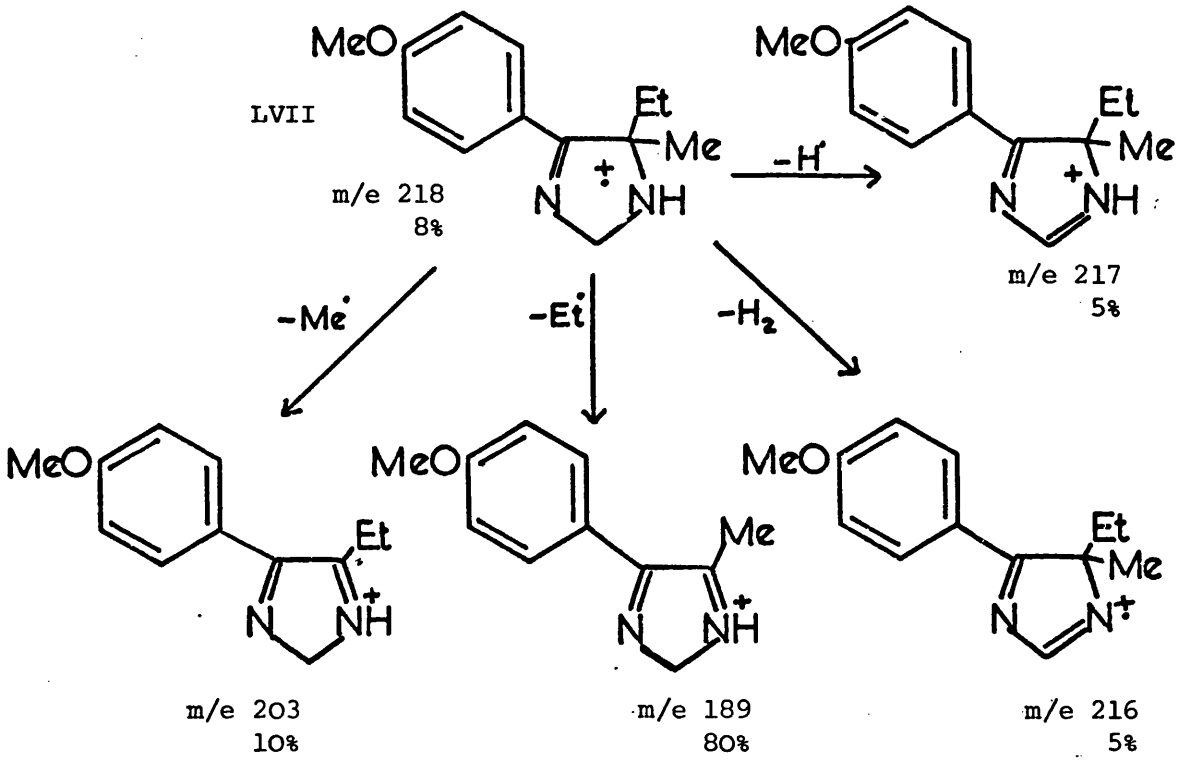
The mass spectra of 3-imidazolines has not been reported in the literature. A paper by Ohashi and co-workers[111] deals only with the fragmentation of 2-imidazolines.

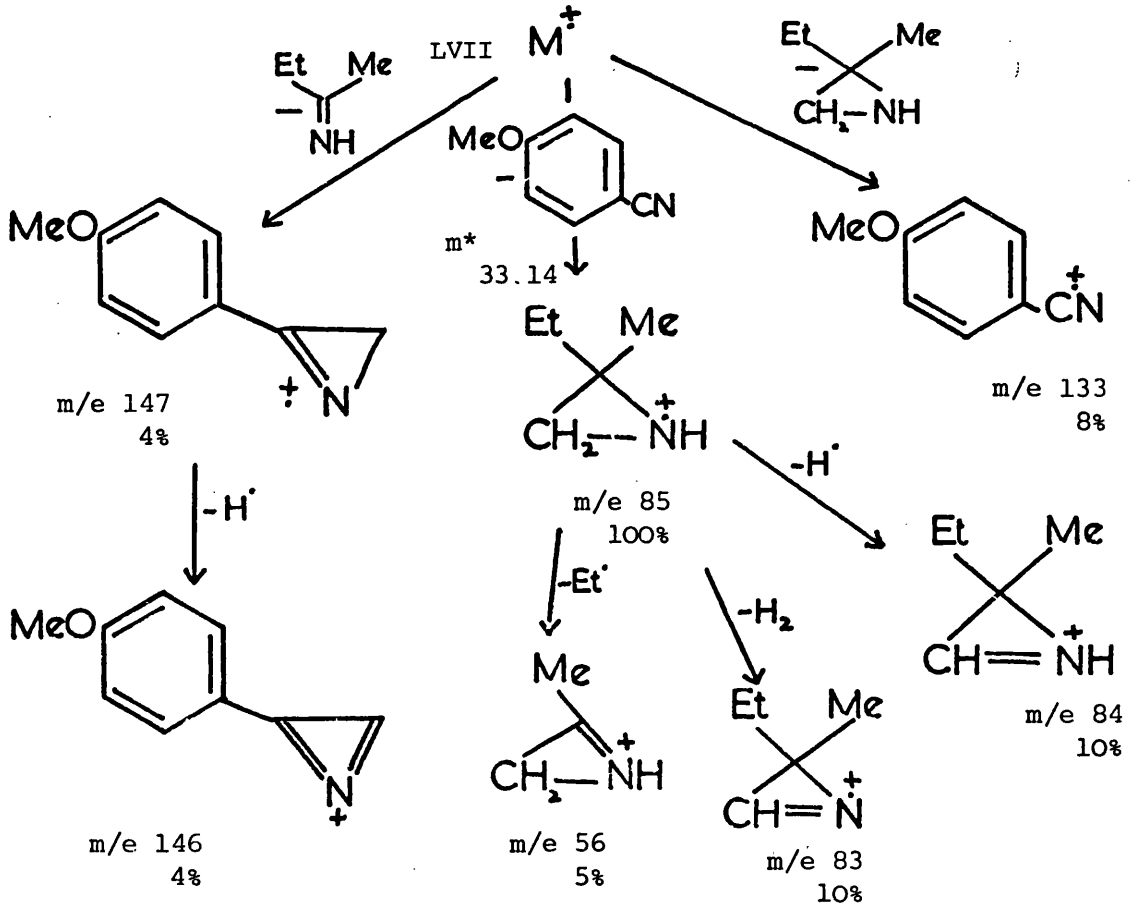
In the compounds with a free -NH group(LV-LVIII) the mass spectrum shows a molecular ion of low intensity (< 7%) from which is

lost a hydrogen ~~ion~~ atom and a molecule of hydrogen. The major fragmentation occurs by two pathways.



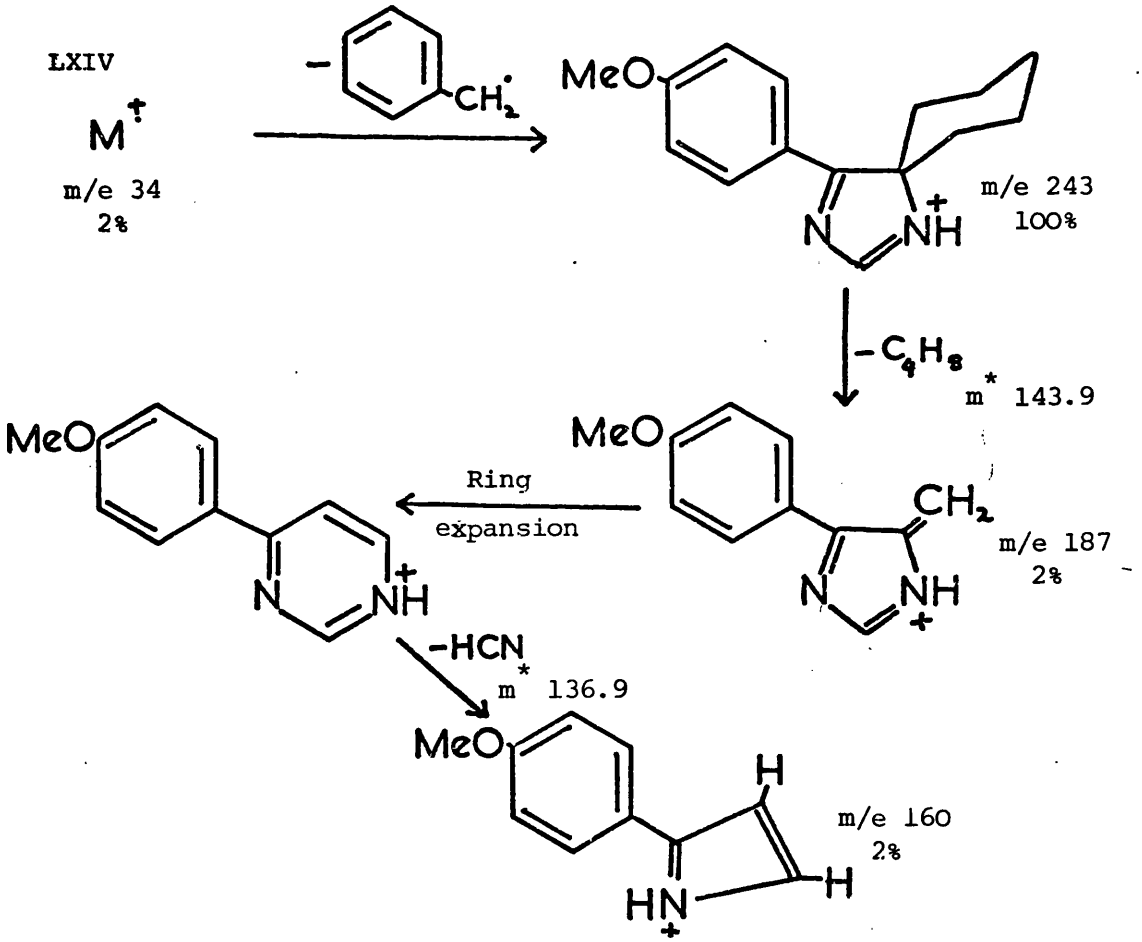
A typical fragmentation is shown by compound LVII on page 53.


LVII
m/e 218
8%
-H·
m/e 217
5%
-Me·
-Et·
-H₂
m/e 203
10%
m/e 189
80%
m/e 216
5%

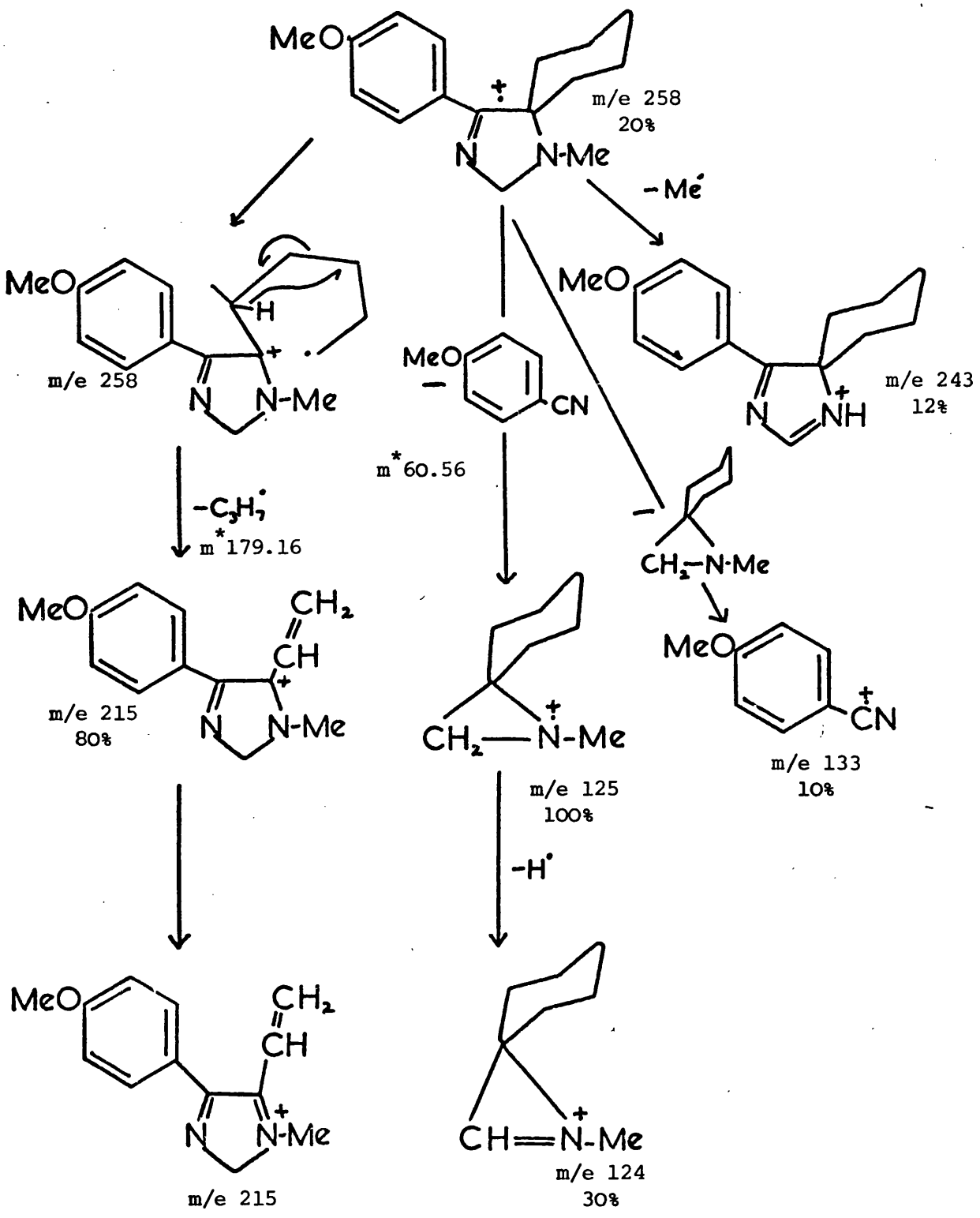

LVII
M+
m*
33.14
m/e 147
4%
m/e 133
8%
m/e 85
100%
-H·
-Et·
-H₂
m/e 146
4%
m/e 56
5%
m/e 83
10%
m/e 84
10%

In compound LV a M-28 ion (40%) was present indicating a loss of ethylene from the cyclopentyl moiety.

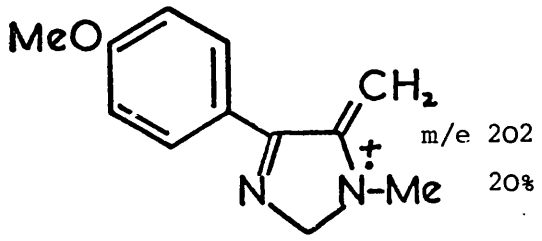
The 2-benzyl imidazoline (LXIV) showed a base peak at M-91 as may be expected. Fragmentation then occurred in the cyclohexyl ring with the loss of butene. The resulting ion, postulated as ring expanding to form a pyrimidine then lost a molecule of HCN. The two latter fragmentations are clearly indicated by metastable peaks.



The imidazolines LIX-LXIII in which the N^1 nitrogen is substituted showed a greater abundance of the molecular ion (>10%). The preferred fragmentation was by degradation of the cycloalkyl group or loss of a methyl radical(LXI) although the base peak in most cases is postulated as an aziridinium ion. An example of such a fragmentation is given by compound LIX.



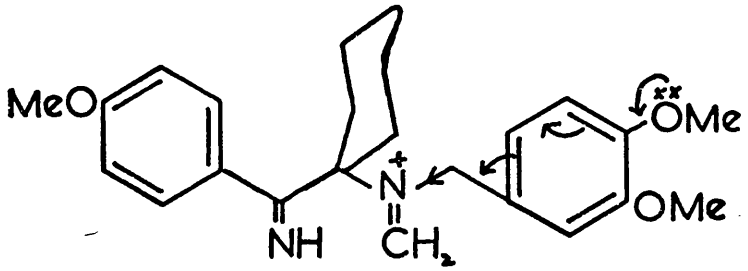
An alternative but less favoured fragmentation of the cyclohexyl ring is the loss of a molecule of butene giving an ion m/e 202.



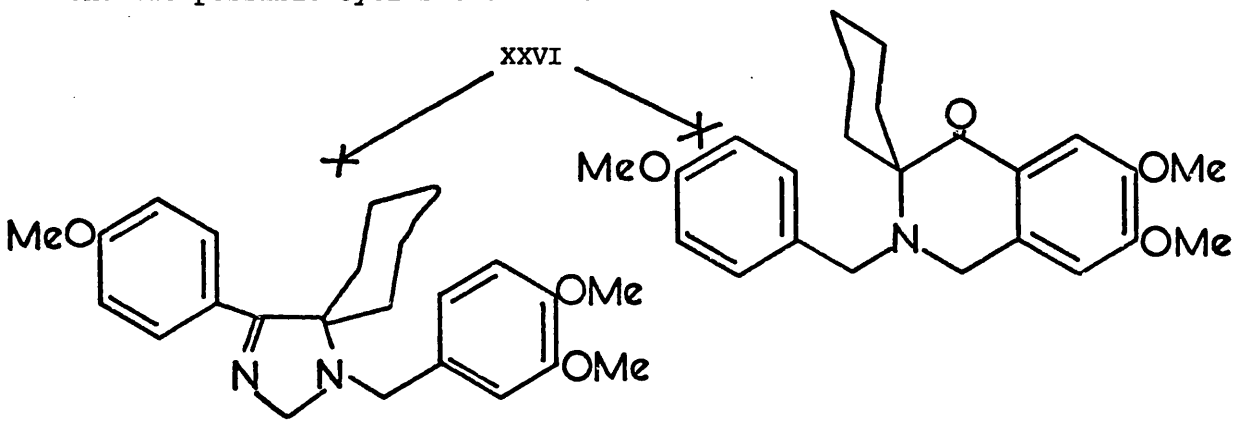
m/e 202

20%

Only two nitriles (XXI and XXVI) failed to give the expected imidazoline on treatment with sulphuric acid. Compound XXI would be expected to give an unstable product according to Kirchner[104] and the result is presented as a formal failure. A possible explanation for the failure of XXVI to give the expected product may be the mesomeric effect of the veratryl moiety lowering the reactivity of the iminium ion.



Alternatively the explanation may lie in the competitive nature of the two possible cyclisations i.e.

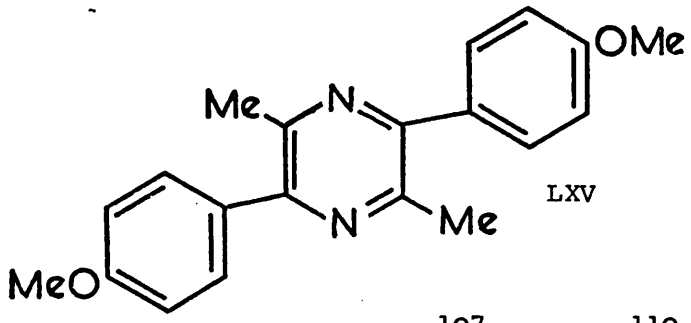


Whatever the true explanation, no identifiable product was obtained.

Nitrile XX reacted to give a mixture of three main products which were separated by column chromatography. They were numbered Fraction 1, Fraction 2 and Fraction 24. None of the products was

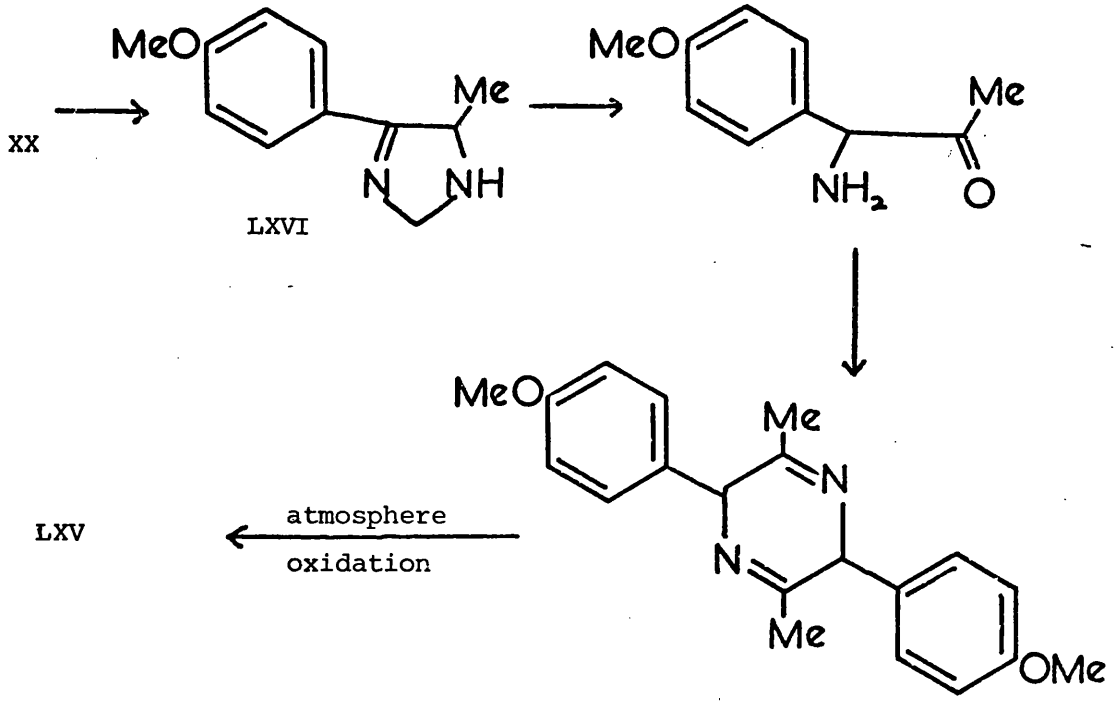
obtained in sufficient purity for elemental analysis but tentative structures were assigned to Fraction 1 and Fraction 24 by the usual spectroscopic techniques.

Fraction 1 is postulated as the substituted pyrazine(LXV).



LXV

In accord with the work of Kirchner[107] and Wells[110] any imidazoline produced from XX would be expected to decompose and the aminoketone so produced to dimerise and oxidise.

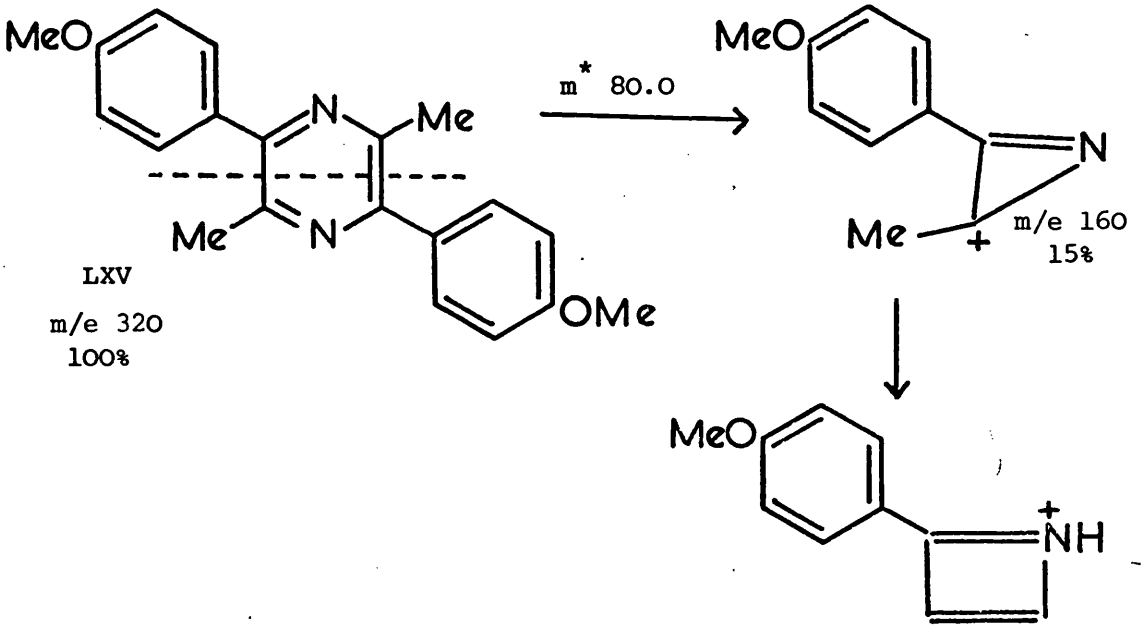


Spectral evidence supports such a structure.

The infra-red spectrum was helpful by negative inference, showing $>$CO and $>$NH or $-$OH groups to be absent, whilst strong absorption at 1220 cm^{-1} and 850 cm^{-1} indicated the presence of -C-O-C (of methoxyl) and paradisubstituted benzene ring respectively.

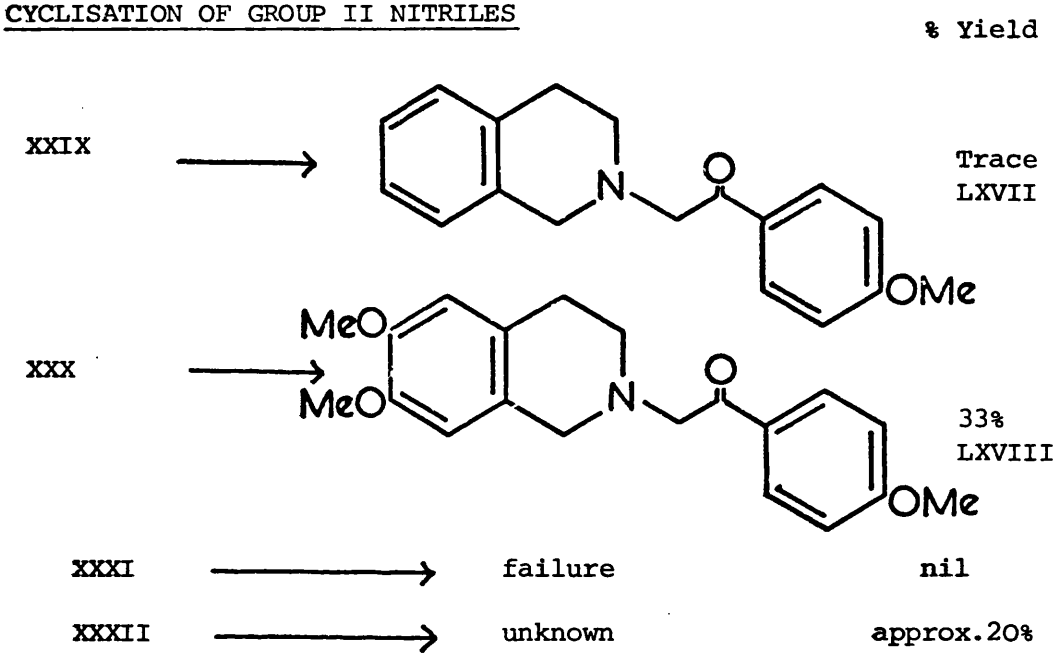
The n.m.r. confirmed the presence of paradisubstituted benzene ring and methoxyl groups and also showed a singlet at δ 2.6 ppm which was assigned to the methyl groups.

Mass spectroscopy confirmed the molecular weight, with the molecular ion as the base peak at m/e 320. A metastable peak at 80.0 strongly suggests cleavage of the molecule into two equal fragments.

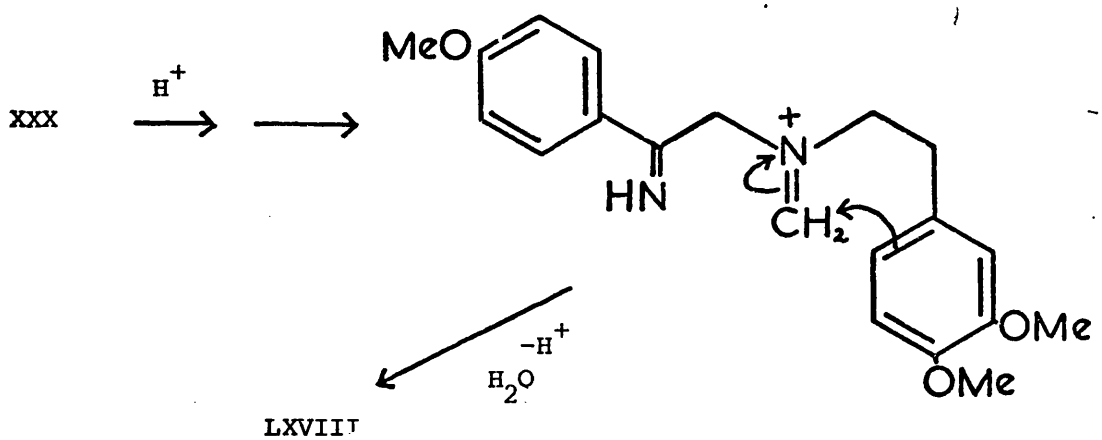


Fraction 27 was given the structure of the undecomposed imidazoline LXVI, infra-red, n.m.r. and mass spectra being comparable with the spectra obtained for the 3-imidazolines previously described.

CYCLISATION OF GROUP II NITRILES



This group of compounds proved to be the most troublesome, only XXX giving an acceptable yield of cyclised product (LXVIII). The formation of LXVIII can be explained by the mechanism previously postulated: i.e.



The structure was unequivocally confirmed by spectroscopy and by an alternative synthesis from 6, 7-dimethoxytetrahydroisoquinoline and 4-methoxyphenacylbromide.

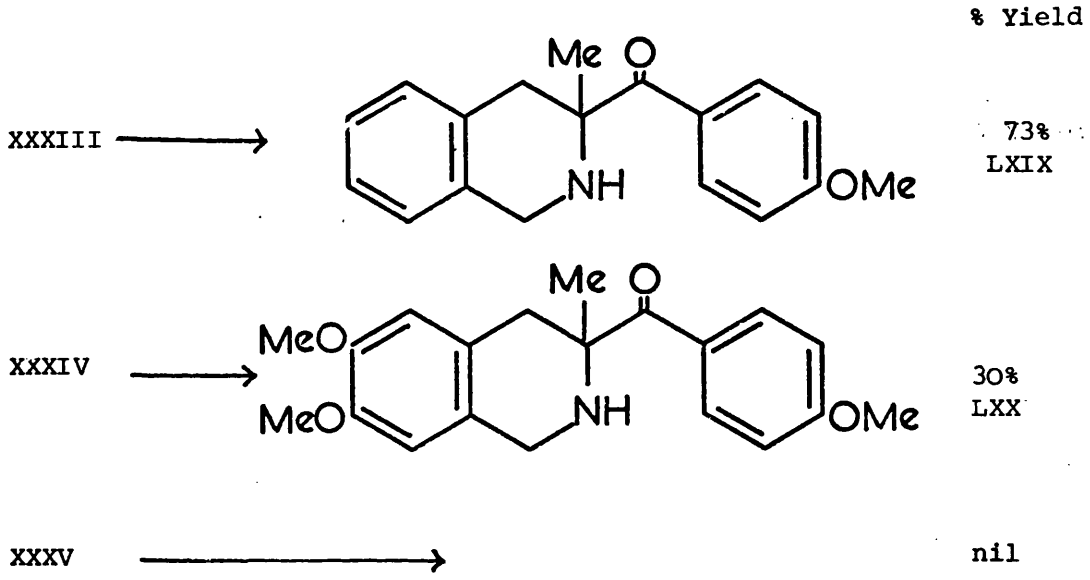
That compound XXIX failed to cyclise is difficult to explain in view of the excellent yield of 3-substituted isoquinoline obtained from nitrile XXXIII. Only a trace of product was obtained, sufficient to use for mass spectroscopy. Evidence from the mass spectrum suggested that cyclisation had taken place.

Nitriles XXXI and XXXII failed to give any identifiable products. Extraction of the diluted and basified reaction mixture from XXXI failed to give a residue on removal of the solvent and no further work was carried out on this compound. Compound XXXII gave a residue after the usual work up procedure but unlike any of the other products, it was completely insoluble in petroleum ether. Recrystallisation was achieved using a mixture of ethylacetate and petroleum ether (1:1). However, the crystals obtained could not be identified.

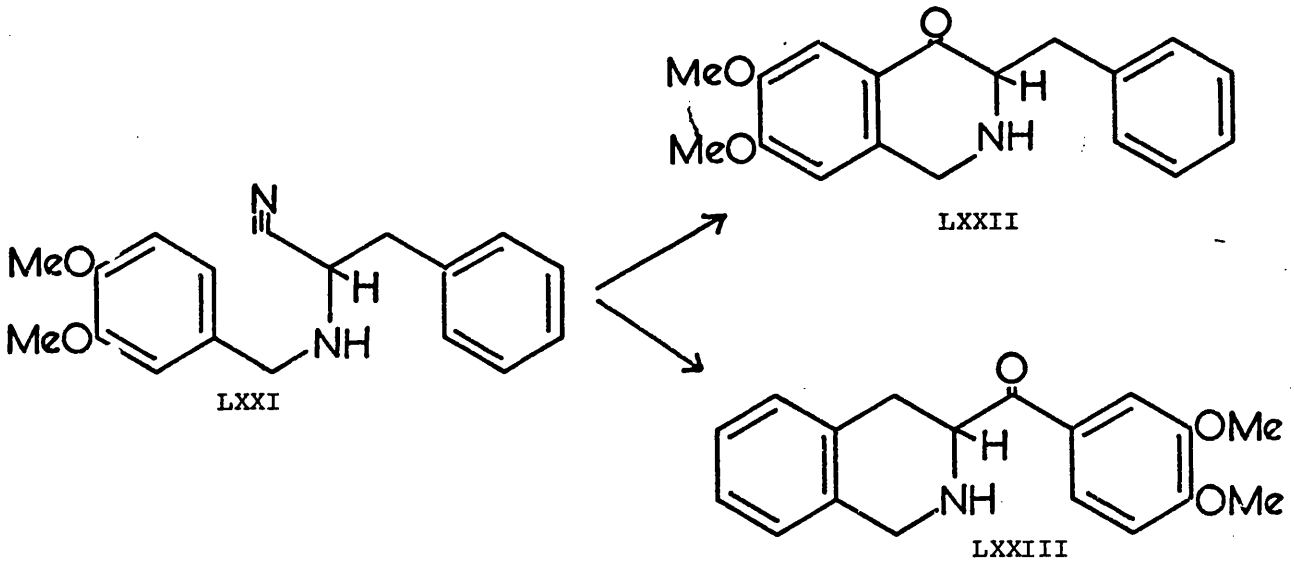
The i.r. spectrum showed a strong broad -OH peak which would obscure any NH absorption. N.m.r. gave an unsatisfactory spectrum with very broad peaks and the mass spectrum showed a molecular ion at m/e 502.

Obviously the reaction had not been successful, possible due to steric hindrance by the cyclohexyl group - although this has not affected the cyclisation when present in other nitriles - and, in the case of XXXI, lack of any activating groups on the nucleophile.

CYCLISATION OF GROUP III NITRILES



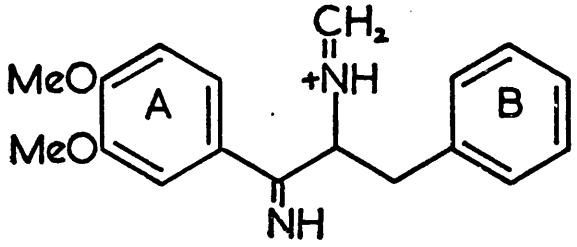
Unpublished work by Waigh[112] has shown that cyclisation of 3.4 dimethoxy nitriles of this type give a mixture of two products.



"With variation of reaction time and temperature the product ratio was never far from 1:1"

That product LXXII is produced may suggest that the mechanism originally postulated by Harcourt and Waigh is operating whilst the formation of LXXIII is in support of the present hypothesis. However, the formation of both compounds may be explained via the same iminium ion, viz:-

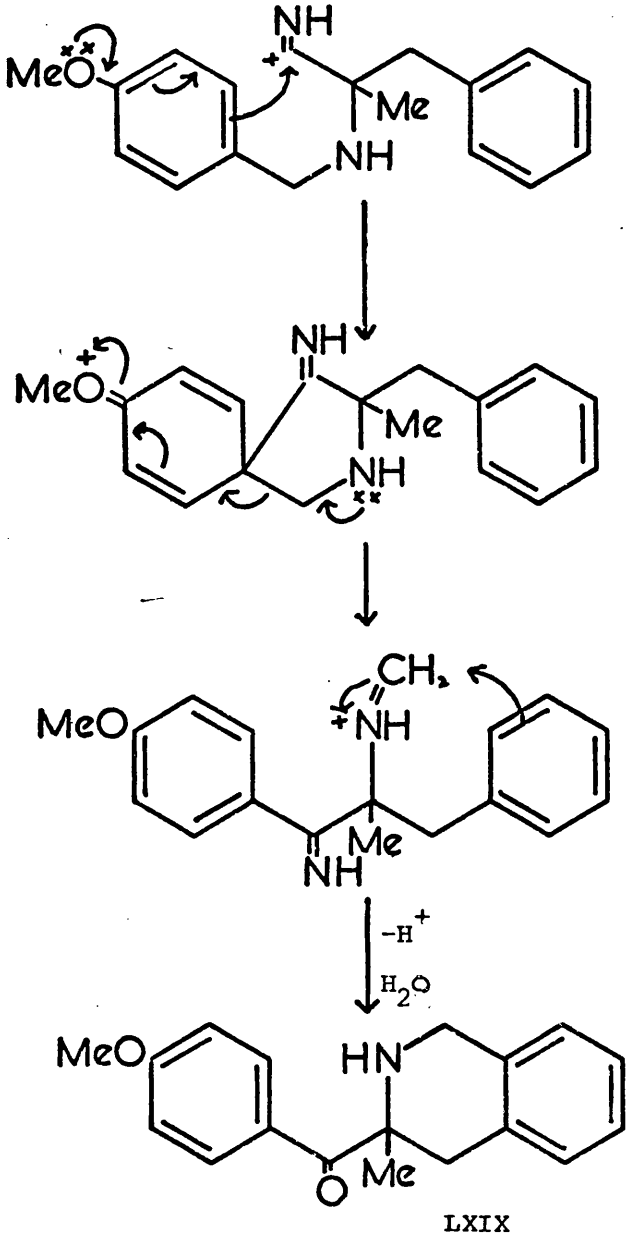
LXXI ⟶ ⟶



If rings A and B have approximately the same nucleophilic power, (the activating effect of the methoxyl groups being offset by the imino group) the cyclisation would occur to ring A or B with equal probability.

The mechanism postulated for the formation of LXIX and LXX is again via an iminium ion.

XXXIII $\xrightarrow{+ H^+}$



LXIX

The variation in yields was surprising. The dimethoxybenzyl nitrile XXXIV gave, in addition to the isoquinoline, a brown solid of indeterminate structure, possibly a polymer. Such a compound could be formed by over activation of the intermediate resulting in an intermolecular reaction.

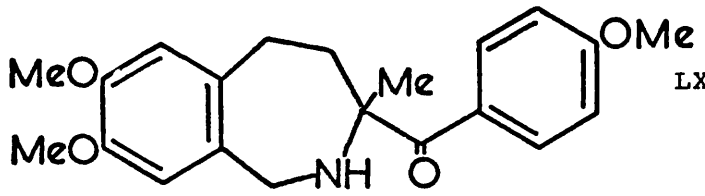
Attempted cyclisation of compound XXV was a failure. The colour changed from green to deep purple during the work up procedure and removal of the solvent gave only an intransigent gum. There is no obvious reason for the failure. If the chlorbenzyl substituent was not a suficiently strong nucleophile to allow cyclisation to the isoquinoline then an imidazoline was expected. In view of the fact that neither was produced again suggests that the reactivity of the iminium ion was affected by the substituents. Assuming this to be true, then, from the results of XXXIV and XXXV cyclisations, the electron availability from the nucleophile is critical.

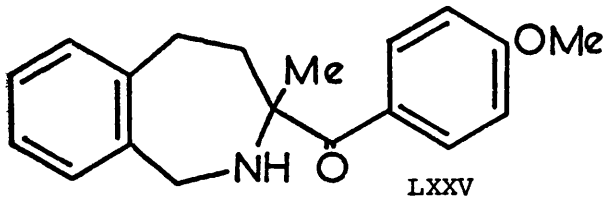
The n.m.r. spectra of LXIX and LXX are unambiguous and very similar, slight differences being caused by the shielding effect of the additional methoxyl groups in LXX.

The mass spectrum of LXIX is of interest in that an ion at m/e M + 1 is clearly shown and confirmed by running spectra at differing pressures. Such an ion is not present in the mass spectrum of LXX although the fragmentation pathways of both compounds are similar.

CYCLISATION OF GROUP 4 NITRILES

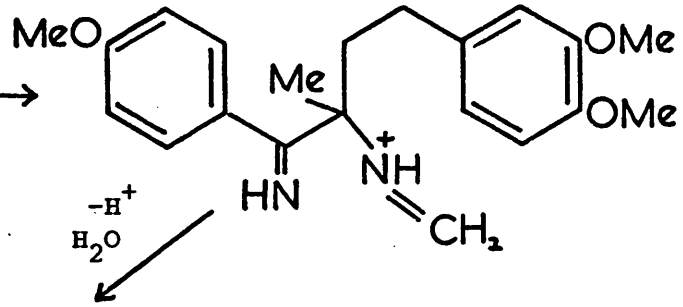
% Yield

XXXVI ⟶  LXXIV 50%

XXXVII ⟶  LXXV 5%

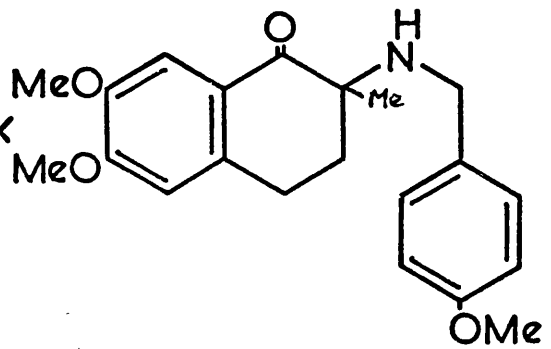
+ a sulphonic acid LXXVI 40%

Cyclisation of XXXVI and XXXVII to yield 2-benzazepines can be explained by the mechanism already postulated:-

XXXVI ⟶ ⟶ 

LXXIV

It is interesting that cyclisation to the 2-benzazepine occurs when the alternative cyclisation to the 1-tetralone LXXVII may have been expected[96], at least as a competing reaction.

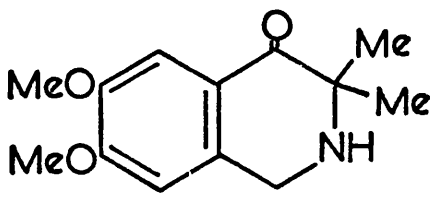
XXXVI ⟶✗ 

LXXVII

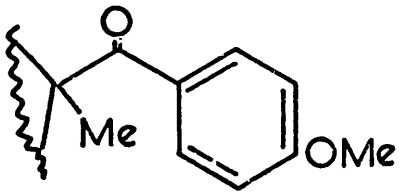
The n.m.r. spectra agree with the structures assigned. The aromatic protons are clearly seen at low field, the methoxyl group(s) giving a strong signal at ca δ 3.8 ppm, the C_1 protons at ca. δ 3.6 ppm and the methyl group at ca. δ 1.4 ppm. The C_4 and C_5 protons give a more complex pattern because of the adjacent chiral centre at C_3 and the (de)shielding effect of the carbonyl and/or the methoxyphenyl group.

Spin decoupling (compound LXXIV) shows one proton of the two adjacent methylene groups to resonate as a high field doublet, overlapping the >NH signal (δ 1.6 ppm) whilst the remaining three protons give a multiplet at δ 2.6 - 3.05 ppm.

Dreiding models show that when the hetero ring exists as a "deformed chair" there is considerable flexibility making a preferred conformation difficult to assign. A possible explanation may be that the conformation is such that one of the C_4 protons is deshielded by the carbonyl group, the other resonating at δ 1.6 ppm. This is in agreement with the findings of Harcourt and Waigh[1] who reported the chemical shift of the methyl protons in 6,7-dimethoxy-3,3-dimethyltetrahydroisoquinolone (LXXVIII) to be at δ 1.3 ppm.

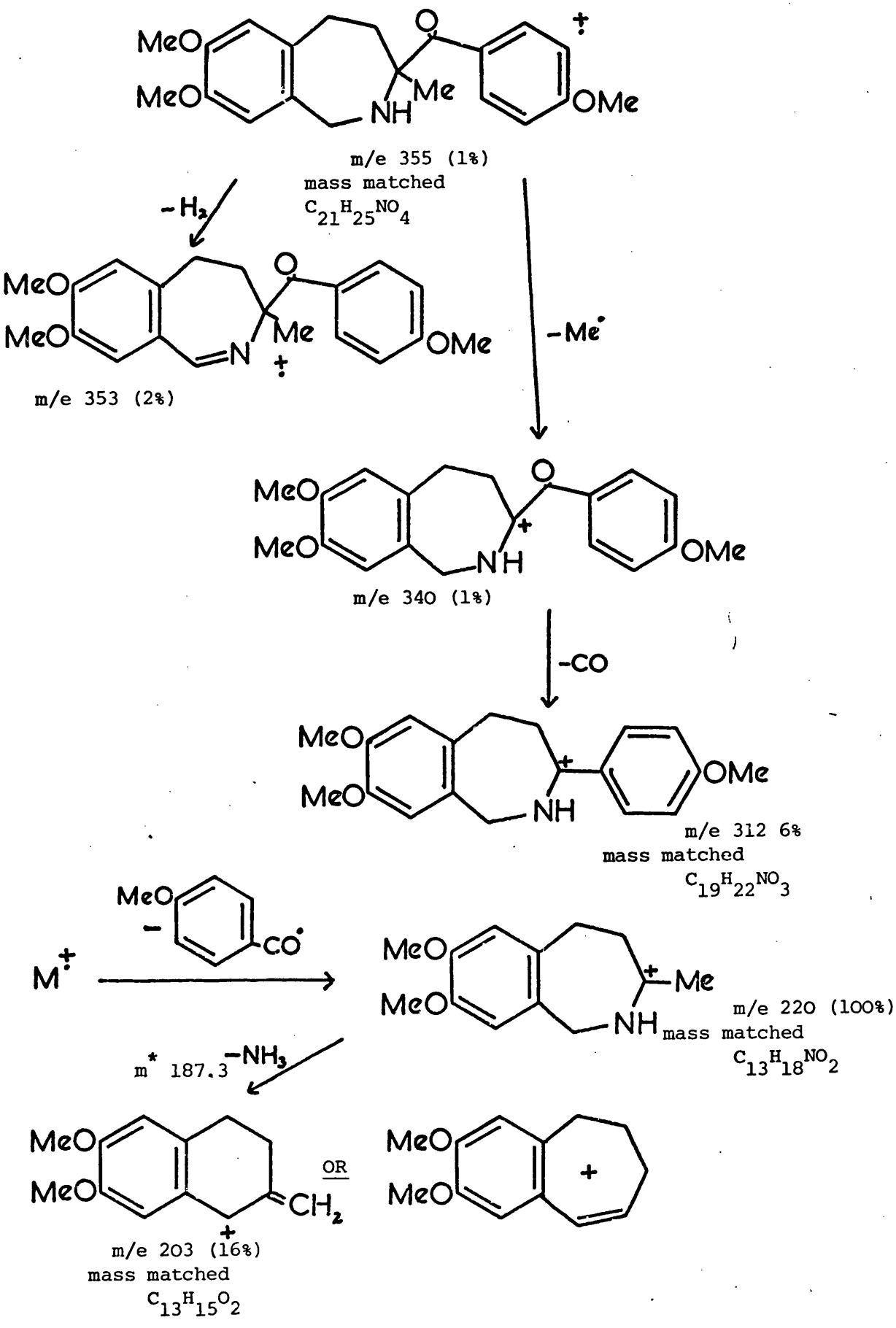


LXXVIII

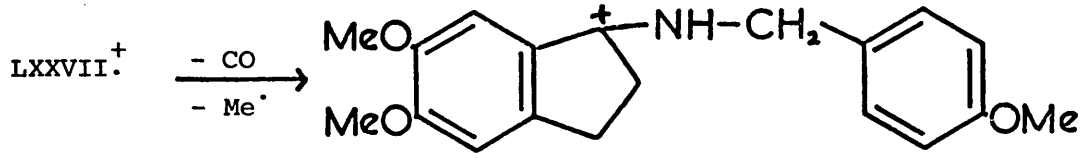


LXXIV

Mass spectrometry of both benazepines showed a fragmentation consistent with the structures assigned. The fragmentation of LXXIV is given as an example on page 66.


MeO
MeO
Me
NH
OMe
m/e 355 (1%)
mass matched
$C_{21}H_{25}NO_4$
$-H_2$
$-Me^{\cdot}$
m/e 353 (2%)
m/e 340 (1%)
-CO
m/e 312 6%
mass matched
$C_{19}H_{22}NO_3$
$M^{+\cdot}$
$-CO^{\cdot}$
m/e 220 (100%)
mass matched
$C_{13}H_{18}NO_2$
m* 187.3
$-NH_3$
OR
CH_2
m/e 203 (16%)
mass matched
$C_{13}H_{15}O_2$

It may be argued that the ion a m/e 312 could be more readily explained by a loss of CO and $CH_3^{\cdot}$ from the tetralone LXXVII.



but there was no other evidence for tetralone formation and t.l.c. showed only a single spot.

The cyclisation of XXXVII proved difficult and the cyclised product LXXV and the (supposed) sulphonic acid LXXVI were isolated from different experiments. The experiment was repeated several times under identical conditions.

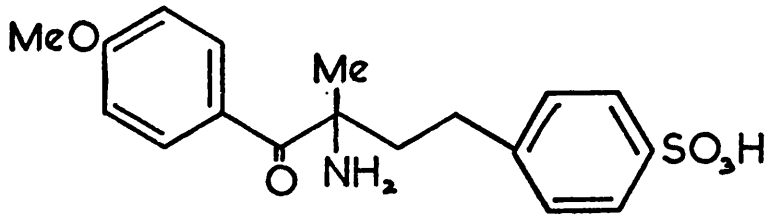
Elemental analysis suggests a tentative molecular formula for LXXVI of $C_{18}\ H_{21}\ NO_5\ S$ but with an unusually large tolerance. A molecular weight could not be determined by mass spectrometry although mass spectrometry was attempted on the free acid and on its tetramethylammonium salt.

Infra-red and n.m.r. spectroscopy were more informative. The i.r. showed strong absorption at γ_{max} 3400 cm^{-1} (-OH), at γ_{max} 1665 cm^{-1} (>CO), at γ_{max} 1170 cm^{-1} and γ_{max} 1010 cm^{-1} (SO_2 asymmetric stretching and SO_2 symmetric stretching respectively), medium absorption at γ_{max} 850 cm^{-1} (para disubstituted benzene ring) and weaker absorption at γ_{max} 690 cm^{-1} (S - O stretching). Any >NH absorption was obscured by the broad-OH band.

N.m.r. spectroscopy showed a strong singlet at δ 2 ppm integrating to three protons (Me group) and a multiplet between δ 2.2 and δ 3.0 ppm integrating to four protons. A 220 MH_z spectrum showed this to be an ABCD pattern indicative of $-CH_2-CH_2-$ unsymmetrically substituted at either end. The signal attributed to the methoxyl protons appeared as a singlet at δ 3.95 ppm. The aryl protons gave two overlapping $AA'XX'$ quartets, each having J values of $9H_z$. Such

signals could be due to two <u>para</u> disubstituted benzene rings, two <u>ortho</u> symmetrically disubstituted benzene rings or one of each. As the solvent used was D_2O/TFA any exchangeable protons e.g. >NH would not be recorded.

From the n.m.r. and i.r. spectra a possible structure for LXXVl could be:



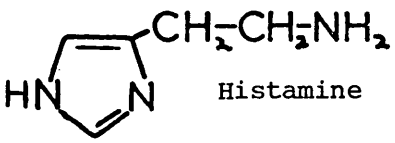
This is not in keeping with such data as is available from the mass spectrum. The mass spectrum shows ions at m/e 121 and m/e 135, mass measured as methoxybenzyl and methoxybenzoyl respectively whilst a third major ion is at m/e 242. Of these three ions, only that at m/e 135 could be formed from the above and the true molecular structure remains undecided.

PHARMACOLOGY

Whilst the primary objectives of the work have been to confirm the postulated reaction mechanism and to evaluate the versatility of the synthesis, many of the new compounds prepared possess structural features of potential biological interest.

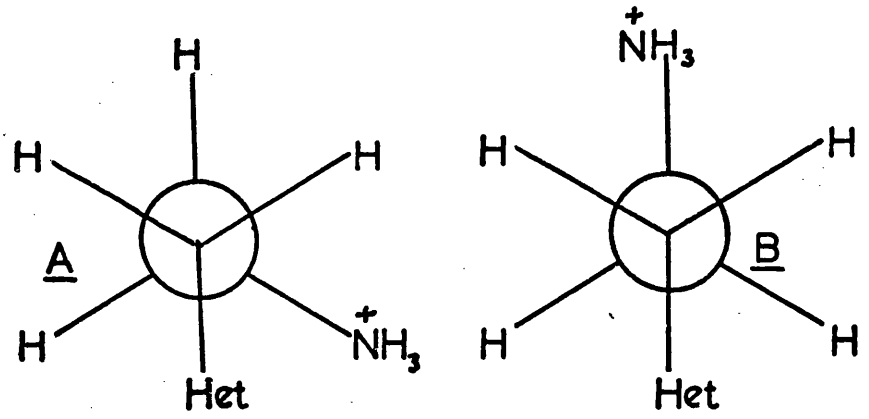
The imidazole ring is to be found in natural products e.g. pilocarpine, histamine and in synthetic drugs. Reduced imidazole systems show many types of biological activity depending on the state of reduction and the substituents present. Much of the work published has been on 2-imidazolines and little is known about biological activity in 3-imidazolines. The compounds prepared by Schulz[109] were claimed to have "marked vasopressor and hypnotic activity and to be non-toxic" but detailed pharmacological results have not been published. The fluorinated amino imidazolines reported by Middleton have shown CNS depressant and muscle relaxant activity but because of the extent of substitution afford little resemblance to the compounds prepared in the present work.

Of contemporary interest is the understanding of the action of histamine at its receptor sites. It is now accepted

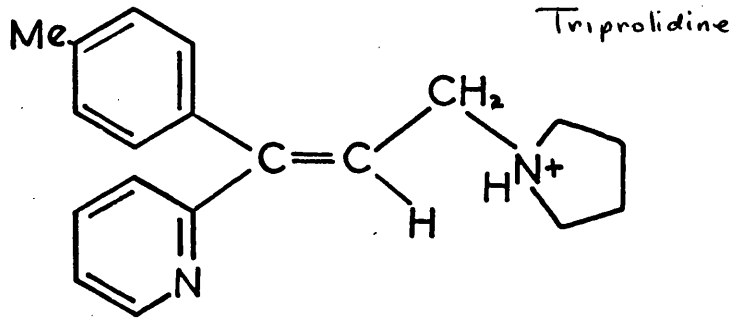


Histamine

that there are two types of histamine receptor in the body[114]. These are designated H_1 (antagonised by known anti-histamine compounds) and H_2 (unaffected by recognised anti-histamine compounds). By a detailed study of n.m.r spectra and molecular orbital calculations various workers [e.g. 115, 116, 117] showed histamine to exist as two different but almost equally preferred skew and anti conformers A and B.



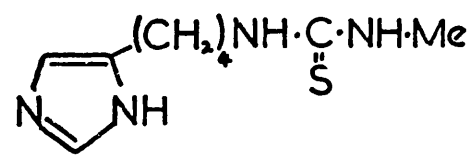
By a comparison of internitrogen distances with the known (H_1) anti-histaminic triprolidine, Kier concluded that conformer B is the H_1 agonist.



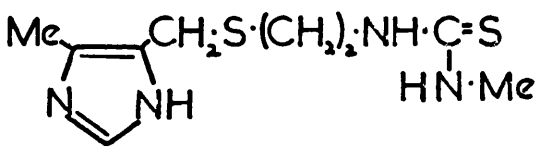
Triprolidine

Later workers are not in agreement with the above statement, since replacement of the pyridyl ring by phenyl does not destroy the H_1 anti-histamine activity.

The early attempts at synthesis of potential histamine H_2-receptor antagonists were unsuccessful. Durant and co-workers having prepared a series of aminoethylimidazopyridines[118] which showed neither agonist nor antagonist activity. Two years later N guanylhistamine was prepared[119] which showed agonist and antagonist activity depending on the concentration. The first reported effective H_2 antagonists were burimamide and metiamide



Burimamide



Metiamide

and successful clinical trials have recently been carried out[120].

The relevance of the above to the present work lies in the biological activity shown by LXII. Although showing little resemblance to metiamide and burimamide LXII administered intravenously at a dose of 6 mg/Kg to two anaesthetised rats during infusion of histamine to stimulate gastric acid secretion, caused a 30-40% reduction in acid output[121]. Unfortunately this effect was not increased at higher doses i.e. a proper dose-response relationship was not established and on this evidence LXII cannot be said to be a true H_2 antagonist for although it interferes with histamine responses this may be that it simply has a toxic action.

No similar activity was shown by other compounds (LVIII, LV, LIX) when subjected to the same test.

A primary screening for analgetic, sedative and hypertension effects was carried out on compounds LVIII, LV, LIX and LXII. These compounds showed no sedative property in mice and only a slight increase in heart rate, lasting about 15 minutes was reported when LVIII was injected intravenously into an anaesthetised dog. Some analgetic activity was shown by LVIII and LIX particularly in the "mouse writhe test".

The writhe tests consists of injecting mice intraperitoneally with phenylquinone (10 um/kg) some thirty minutes after treatment with the substance under test, and comparing the number of writhes with those of mice similarly injected but given a known analgesic, in this case codeine (40 um/kg). The results of such a test are given below[122]:-

Total number of writhes

LIX 400 µm/kg orally	water	codeine 40 µm/kg
35	187	99
% inhibition 81.3%		47.1%

Also testedfor analgetic activity was compound LXXIV This compound showed some analgetic properties in both the writhe test and the 55° hot plate test. Unfortunately,that LXXIV caused marked stimulation at analgetic doses,precluded it from any further pharmacological study.

CONCLUDING DISCUSSION

Suggestions for Further Work

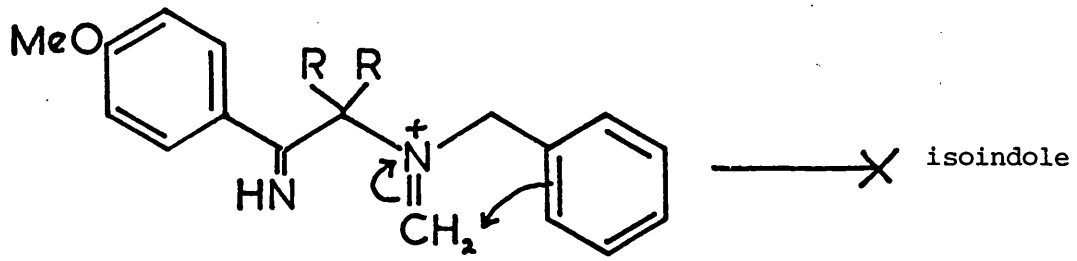
Sulphuric acid treatment of 4-methoxybenzylamineoacetonitriles does not yield the acid or amide as might be expected from a consideration of classical reaction mechanism. The reaction proceeds via a spiro intermediate produced by electrophilic attack *para* to the C_4 methoxy substituent followed by formation of an iminium ion, the fate of which appears to depend upon the availability of nucleophilic sites within the molecule. Although attempts to trap the iminium ion by intermolecular reaction with alternative nucleophiles have failed, the proposed mechanism accounts for the formation of a variety of N-heterocyclic compounds. Most of the compounds prepared are original and not readily accessible by alternative syntheses. Thus structural assignment has very largely been based upon spectroscopic data which, with few exceptions has proved unambiguous. N-phenacyl-tetrahydroisoquinolines are readily prepared from the parent heterocycle and here confirmation of structure by a completely unambiguous synthesis was achieved (LXVIII).

A study of the cyclisation of the 3,4,5-trimethoxybenzylamino-acetonitrile (XII) shows that "normal" cyclisation involving electrophilic attack *para* to the C_3 methoxy substituent also occurs. However, formation of the 7-hydroxy-6,8-dimethoxyisoquinoline (LI) is difficult to explain without the formation of the spiro intermediate. That such an intermediate is formed is in agreement with the benzoylbenzoic acid re-arrangements previously discussed and which were carried out in a like solvent. Jackson and co-workers[123] discount such an intermediate in a study of the decomposition of N-benzyl-N-tosylaminoacetaldehydes to the corresponding N-tosyl-

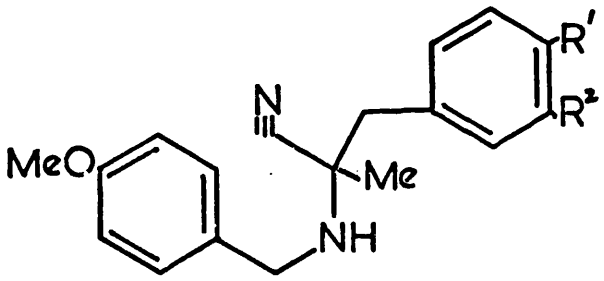
benzylamines. As these workers were using dilute hydrochloric acid/dioxan as the solvent a comparison with the present work is not realistic.

It is not possible at this stage to state by which mechanism (or whether by both mechanisms) the cyclisation of 3,4-dimethoxybenzylaminoacetonitriles to 6,7-dimethoxyisoquinolinones[1] proceeds. It is anticipated that the cylisation of, for example, 3-ethoxy-4-methoxybenzylaminoacetonitriles would yield the 6-ethoxy-7-methoxyisoquinolinone (via the spiro intermediate) or/and the 7-ethoxy-6-methoxyisoquinolinone (by "normal" cyclisation). Investigation by n.m.r. spectroscopy for long range coupling (or nOe) between the O-methyl and O-methylene protons and the aromatic protons should resolve the problem.

In view of the interesting biological activity shown by the 1-benzylimidazoline (LXII) it is of vital significance to obtain a measure of the nature and strength of the biological response with variation of the 1-substituent. Although the parent imidazoline had been obtained in excellent yield (80%)[49] it proved surprisingly resistant to benzylation. Likewise attempts to N-benzylate the aminonitrile were unsuccessful. It therefore appears necessary, in the present state of knowledge, to introduce the N-substituent prior to nitrile formation. This is readily achieved by imine formation and subsequent reduction, but the secondary amines thus obtained did not react wholly satisfactorily in the Strecker nitrile synthesis. In the cyclisation of nitriles of this group the possibility of formation of a dihydroisoindole may be considered but no evidence for such a compound was found.



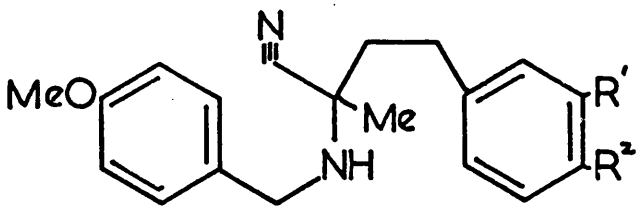
The behaviour of the 2-benzylpropionitriles (XXXIII - XXXV) on treatment with sulphuric acid is difficult to explain. Here it was anticipated that competition between isoquinoline formation and the most likely alternative, production of a 5-benzylimidazoline would be revealed by modification of the nucleophilic character of the phenyl substituent.



			Yield	
	R'	R^2	isoquinoline	imidazoline
XXXIII	H	H	73%	nil
XXXIV	OMe	OMe	30%	nil
XXXV	Cl	H	nil	nil

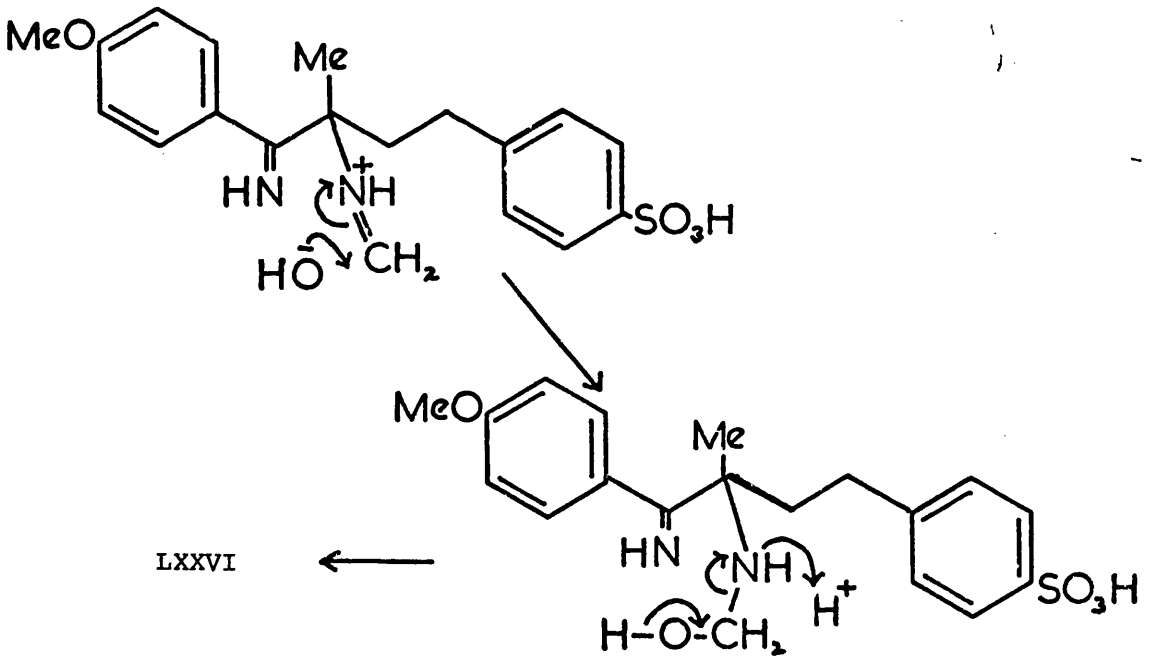
Increasing the nucleophilic character of the ring reduced the yield of isoquinoline presumably due to competing sulphonation of the dimethoxy ring. Decreasing the nucleophilic character resulted in formation of neither the isoquinoline nor the imidazoline. There do not appear to be any obvious steric or electronic factors precluding formation of the benzylimidazoline.

A completely anomolous situation is seen in the cyclisation of the phenylbutyronitriles (XXXVI, XXXVII),



	R'	R^2	Yield Benzazepine	
XXXVI	OMe	OMe	50%	LXXIV
XXXVII	H	H	5%	LXXV

where the strongly nucleophilic dimethoxy ring gives a 50% yield of the benzazepine whilst the less nucleophilic phenyl moiety is sulphonated, yielding only 5% of benzazepine. If it is assumed that cyclisation to the benzazepine does not occur because of deactivation of the phenyl moiety by sulphonation the question then arises as to why an imidazoline is not formed. The formation of the postulated sulphonic acid LXXVI can be explained by hydrolysis of the iminium ion after sulphonation:-



but the question remains unanswered.

As a synthetic route to 3-imidazolines the work offers a degree of flexibility with regard to substituents in the 1,2 and 5 positions on the imidazoline ring but is limited at the present stage to a

4-methoxyphenyl substituent at C_4. Replacement of the methoxyl group by a dimethylamino gave the amide but there is no obvious reason why an alternative activated aromatic system could not be employed. Substituents at C_5 could be more easily varied as ketones containing a second reactive group are readily available.

Of particular interest would be the introduction of basic substituents into the imidazoline ring together with an attempt to correlate pKa and lipophilicity with H_2-antagonist activity. Imidazolines may also be exploited as a framework for ergothioneine analogues and the work extended further to include the synthesis of imidazoline propionic acid derivatives and their assessment as GABA mimics.

EXPERIMENTAL

Infra-red spectra were recorded on a Unicam S.P.200 spectrophotometer as potassium bromide discs or liquid films, for solids and liquids respectively. Values are given as ν_{max} (cm^{-1}) and are quoted on grounds of significance rather than intensity. N.m.r. spectra were recorded on a Varian A100 spectrometer at the Physico-chemical Measurements Unit, Harwell and on a JEOL PS100 instrument at the School of Chemistry, University of Bath. Chemical shifts were measured in p.p.m. downfield from tetramethylsilane as internal standard. The following abbreviations have been employed: Int (= relative integrated intensity), mult. (= multiplicity, where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The term "deuteration" has been used throughout to signify that a solution was shaken with deuterium oxide to effect exchange of hydrogen for deuterium.

Mass spectra were recorded at the School of Chemistry, University of Bath using an A.E.I. MS12 mass spectrometer. Precision mass measurements were carried out by the Physico-chemical Measurements Unit, Harwell. With the exception of chlorine-37 isotope peaks have not been quoted. Meta stable peaks are indicated as m*.

Elemental analyses were carried out by the Butterworth Microanalytical Consultancy Limited, Teddington.

Melting points were taken on a Kofler hot-bench and are corrected.

4-methoxybenzylamine (anisylamine) hydrochloride

Anisaldehyde (0.1 mole), hydroxylamine hydrochloride (0.1 mole) and sodium acetate (0.2 mole) were dissolved in alcohol 70% (500 ml) and refluxed on a steam bath for 4 hours. The reaction mixture was cooled and 2N aqueous sodium hydroxide (500 ml) added. Raney alloy (40g.) was added in portions to the stirred solution and the stirring continued until evolution of hydrogen had ceased. The solid was filtered off and the filtrate extracted three times with chloroform. The combined chloroform extracts were washed once with water, dried ($Mg\ SO_4$) and the chloroform removed. The residue was dissolved in dry ether and an excess of dry hydrogen chloride passed into the solution, precipitating the amine hydrochloride. This was crystallised from alcohol ether mixture (1:1) as prisms.

Yield 12g (69.5%) m.p. 228° (lit[224] quotes 230-1°)

Also prepared by this method was

4-dimethylaminobenzylamine hydrochloride

Prepared from 4-dimethylaminobenzyladehyde 0.1M

Yield 12.5g (67.2%) m.p. 200(d)

as base hydrchloride.

The base picrate was obtained as yellow needles from methanol and had m.p. 190° (d) (lit. quotes[125] 187-189°d).

N-methyl-4-methoxybenzylamine hydrochloride

Anisaldehyde (136g; 1.0 mole) was dissolved in ethanol 95% (1l) and 33% $^{W}/_{V}$ methylamine in alcohol (120 mls i.e. an excess) added slowly. The mixture was allowed to stand for approximately 36 hours. Sodium borohydride (50g) was added in portions and after standing for a further 24 hours the reaction mixture was refluxed on a waterbath. After cooling dilute hydrochloric acid was cautiously added to destroy the excess sodium borohydride until the solution was acid to litmus, basified with 5N sodium hydroxide and extracted three times with chloroform. The combined chloroform extracts were washed once with water, dried (Mg SO_4) and the chloroform removed. The residue was dissolved in dry ether and dry hydrogen chloride passed into the solution, precipitating the amine hydrochloride. The product was recrystallised from alcohol/ether mixture as prisms m.p. 166° (lit.quotes[126] 166°)

Yield 135g (72%)

General method for preparation of N-substituted 4-methoxy-benzylamines.

Equimolecular quantities of amine and aldehyde were dissolved in dry benzene and refluxed in a Dean Stark apparatus until the theoretical amount of water had been collected. The solvent was removed, the residue dissolved in aqueous alcohol and an excess of sodium borohydride added in small protions. After standing overnight the mixture was refluxed, the remaining borohydride destroyed by addition of dilute hydrochloric acid until the clear solution was acid to litmus. The solution was basified with 5N

sodium hydroxide solution and extracted with three 50 ml portions of chloroform. The combined chloroform extracts were washed once with water, dried ($MgSO_4$) and the chloroform removed. The residue was dissolved in dry ether and dry hydrogen chloride passed into the solution, precipitating the amine hydrochloride which was collected and recrystallised from absolute alcohol/ether mixture.

Compounds prepared by this method:-

N-benzyl-4-methoxybenzylamine hydrochloride

4-methoxybenzaldehyde 0.1 M

benzylamine 0.1 M

Yield 18.0g (49.5%) as base hydrochloride (prisms)

m.p. 215° (lit.[127] quotes 214-215°)

N-veratryl-4-methoxybenzylamine hydrochloride

4-methoxybenzaldehyde 0.1 M

veratrylamine 0.1 M

Yield 26g (80.4%) as base hydrochloride (prisms)

m.p. 255°

	C	H	N	Cl
Found	63.41	6.70	4.20	10.87%
$C_{17}H_{21}NO_3HCl$ requires	63.06	6.80	4.33	10.97%

N-(4-methoxybenzyl)-2-phenethylamine hydrochloride

4-methoxybenzaldehyde 0.1 M

2-phenethylamine 0.1 M

Yield 21.5g (77%) as base hydrochloride (prisms)

m.p. 256-258° (lit.[128] quotes 266-267°).

N-(4-methoxybenzyl)-2(3,4-dimethoxyphenyl)-ethylamine hydrochloride

Prepared from 4-methoxybenzaldehyde 0.1 M

homoveratrylamine 0.1 M

Yield 22.2g (65.8%) m.p. 217°

(as base hydrochloride) (lit.[129] quotes 234°).

1-(4-methoxyphenyl)-2-phenethylamine hydrochloride

Phenylacetic acid (27.2g, 0.2 M) was mixed with anisole (21.6g, 0.2 M) and PPA (200g) and heated on a boiling waterbath for 3 hours, stirring continuously. The mixture was then poured into water, basified with 5N NaOH, cooled and filtered. The residue was recrystallised from methanol as small needles giving 27.5g (60.8%) of 4'-methoxydeoxybenzoin m.p. 70° (lit.[130] quotes 78°).

4'-methoxydeoxybenzoin (11.3g, 0.05 M) was refluxed in methanol (150 ml) for 6 hours with hydroxylamine hydrochloride (5g) and sodium acetate (10g), after which time a small sample was removed, and diluted with an equal part of water. On cooling this gave white acicular crystals m.p. 119° (lit.[130] quotes 4'methoxydeoxybenzoin oxime m.p. 111°).

The remaining reaction mixture was basified with 5N NaOH (350 ml) and nickel/aluminium alloy powder (20g) added in small portions with continuous stirring. When evolution of hydrogen ceased the solution was filtered and the filtrate extracted with 3 x 100 ml portions of chloroform. The combined chloroform extracts were washed once with water (10 ml), dried ($MgSO_4$) and the chloroform removed. The residual oil was dissolved in dry ether and dry hydrogen chloride passed in giving a white precipitate of amine hydrochloride. Recrystallisation from ethanol/ether mixture (1:1) gave 10g (76%) of 1-(4-methoxyphenyl)-2-phenethylamine hydrochloride m.p. 220° (lit.[131] quotes 215-217°).

4-chlorophenylacetone

4-chlorobenzaldehyde (35g, 0.25 M), nitroethane (19g, 10% excess) and n-butylamine (10 ml) were refluxed with toluene (150 ml) in a Dean-Stark apparatus until no more water was produced. A 3 l. 3 necked round bottom flask was equipped with two reflux condensers, heating mantle, dropping funnel and high speed stirrer.

The toluene solution was transferred to the flask and water (200 ml), iron powder (100g) and ferric chloride (2g) added. With vigorous stirring the mixture was heated to 75°C and concentrated hydrochloric acid (200 ml) added over a 2 hour period. Heating and stirring were continued for a further 30 minutes.

The suspension was transferred to a 2 l. flask and steam distilled until 5 l. of distillate had been collected. The toluene layer was separated and the aqueous layer extracted with 3 x 100 ml portions of toluene. The combined toluene solutions were agitated for 30 minutes with a solution of sodium hydrogen sulphite (13g) in

water (200 ml) and the aqueous layer removed. The toluene solution was washed with water (50 ml), dried ($MgSO_4$) and the toluene removed under reduced pressure, yielding 4-chlorophenyl-acetone (21g, 50%, n_D^{20} 1.5380; lit. quotes [132] n_D^{20} 1.5328).

General method for the preparation of substituted benzylamino nitriles.

To a solution of amine hydrochloride (0.1 mole) in water (400 ml) was added a few drops of dilute hydrochloric acid. The carbonyl compound (0.1 mole) was added and, while stirring vigorously, sufficient alcohol (95%) was added to give a homogeneous solution. Potassium cyanide (10g) in water (50 ml) was added dropwise and vigorous stirring continued until the solid benzylaminonitrile separated out or up to a maximum of 72 hours. The product was either filtered off or extracted with chloroform as appropriate, washed thoroughly with water, dried and recrystallised from petroleum ether (b.p. 60-80°).

When the product would not crystallise, preparation of the hydrochloride was attempted by passing dry HCl gas into a solution of the nitrile in dry ether, filtration of the precipitated hydrochloride and re-crystallisation from alcohol/ether mixture (1:1).

Compounds prepared by this method:

2-(4-methoxybenzylamino)-2-spirocyclohexylacetonitrile [49] (1)

2-(4-methoxybenzylamino)-2-spirocyclopentylacetonitrile (XVI)

Using 0.05 molar quantities

Yield 9.7g (84%) as small colourless prisms.

m.p. 67°

	C	H	N
Found	73.19	7.92	12.15%
$C_{14}H_{18}N_2O$ requires	73.06	7.81	12.17%

i.r. >NH 3250 cm^{-1}

- C ≡ N 2200 cm^{-1}

n.m.r.

	int.	mult.	assignment
1.45	1*	s	>NH
1.70 - 2.20	8	mult.	cyclopentyl
3.76	2	s	benzylic CH_2
3.80	3	s	methoxyl
6.79 - 6.86	2	d(J=9Hz)	) asymmetrical
7.20 - 7.27	2	d(J=9Hz)	) para disubstituted) benzene ring.

* disappeared after deuteration

Mass spectrum

M^+ m/e 230 (10%); m/e 229(8%); m/e 203 (8%)

m/e 136 (5%); m/e 121 (100%)

m^* 72.0

2-ethyl-2-(4-methoxybenylamino)-butyronitrile (XVII)

Using 0.05 molar quantities

Yield 8.8g (82%) as small colourless prisms.

m.p. 51°

		C	H	N
Found		72.66	8.84	11.80%
$C_{14}H_{20}N_2O$ requires		72.41	8.62	12.07%

i.r. >NH 3350 cm^{-1}

- C ≡ N 2250 cm^{-1}

n.m.r. (spectrum - page 134)

	int.	mult.	assignment
0.9 - 1.15	6	t(J=7Hz)	$(CH_3 - CH_2)_2$
1.35	1*	s	>NH
1.60 - 1.90	4	(J=7Hz)	$(CH_3 - CH_2)_2$
3.80	5	s	benzylic CH_2 + methoxyl
6.80 - 6.95	2	d(J=9Hz))	asymmetrical para disubstituted benzene ring.
7.20 - 7.35	2	d(J=9Hz))	

* disappeared after deuteration

Mass spectrum

M^+ m/e 232 (5%); m/e 231 (2%); m/e 205 (10%);

• m/e 136 (2%); m/e 121 (100%).

m^* 71.42

2-(4-methoxybenzylamino)-2-methylbutyronitrile (XVIII)

Using 0.05 molar quantities

Yield 9.3g (87%) as a yellow thermolabile oil.

The base hydrochloride (m.p. 179° d) was prepared for elemental analysis.

	C	H	N	Cl
Found	61.03	7.40	10.88	13.92%
$C_{13}H_{18}N_2O.HCl$ requires	61.30	7.46	11.00	13.95%

i.r. (base) >NH 3220 cm^{-1}

- C ≡ N 2200 cm^{-1}

n.m.r. (base) (spectrum - page 135)

	int.	mult.	assignment
0.96 - 1.16	3	t(J=7Hz)	CH_3 - CH_2-
1.40 - 1.52	4*	s	>NH + - CH_3
1.62 - 1.88	2	(J=7Hz)	CH_3 - CH_2-
4.74	2	s	benzylic CH_2
4.86	3	s	methoxyl
6.78 - 6.92	2	d(J=9Hz))	asymmetrical para
7.18 - 7.32	2	d(J=9Hz))	disubstituted benzene ring.

* reduced to 3 after deuteration.

Mass spectrum

M^+ m/e 218 (5%); m/e 191 (10%); m/e 136 (10%); m/e 121 (100%).

2-(4-methoxybenzylamino)-2-methylpropionitrile (XIX)

Using 0.05 molar quantities.

Yield 7.4g (72%) as small white prisms.

m.p. 66°

	C	H	N
Found	70.57	8.03	13.72%
$C_{12}H_{16}N_2O$ requires	70.60	7.85	13.73%

i.r. $>NH$ 3340 cm^{-1}

$-C \equiv N$ 2250 cm^{-1}

n.m.r. (spectrum - page 136)

	int.	mult.	assignment
1.45	7*	s	2 x CH_3 + $>NH$
3.76	2	s	benzylic CH_2
3.80	3	s	methoxyl
6.78 - 6.92	2	d(J=9Hz)	asymmetrical para disubstituted benzene ring.
7.18 - 7.34	2	d(J=9Hz)	

* reduced to 6 after deuteration.

Mass spectrum

M^+ m/e 204 (8%); m/e 203 (3%); m/e 177 (10%);

m/e 136 (5%); m/e 121 (100%).

m^* 155; m^* 82.5

2-(4-methoxybenzylamino)-propionitrile (XX)

Using 0.05 molar quantities.

Yield 8.3g (87%) as a pale yellow thermolabile oil.

The base hydrochloride (m.p. 160° d), as fine white prisms was prepared for elemental analysis.

	C	H	N	Cl
Found	58.50	6.68	12.29	15.70%
$C_{11}H_{14}N_2O$ HCl requires	58.28	6.62	12.36	15.67%

i.r. (base) $>NH$ 3350 cm^{-1}

$-C \equiv N$ 2250 cm^{-1}

n.m.r. (base)

	int.	mult.	assignment
1.45 - 1.65	4*	d with shoulder (J=8Hz)	$-CH_3$ + >NH
3.60	1	q (J=8Hz)	CH - CH_3
3.80	3	s	methoxyl
3.90	2	s	benzylic CH_2
6.80 - 6.90	2	d(J=9Hz))	asymmetrical para disubstituted ring
7.20 - 7.30	2	d(J=9Hz))	

*reduced to 3 after deuteration.

On irradiation at δ 3.60 ppm the doublet at 1.45 - 1.65 ppm became a singlet.

Mass spectrum

M^+ m/e 190 (4%); m/e 189 (3%); m/e 163 (12%); m/e 136 (2%); m/e 121 (100%).

2-(4-methoxybenzylamino)-acetonitrile (XXI)

Using 0.05 molar quantities.

Yield 7.9g (90%) as a pale yellow thermolabile oil.

The base hydrochloride (fine colourless prisms m.p. 172° d) was prepared for elemental analysis.

	C	H	N	Cl
Found	56.73	6.20	12.96	16.73%
$C_{10}H_{12}N_2O.HCl$ requires	56.50	6.13	13.20	16.70%

i.r. (base) >NH 3350 cm^{-1}

$-C \equiv N$ 2250 cm^{-1}

n.m.r. (base)

	int.	mult.	assignment.
1.60 - 1.80	1*	broad s	>NH
3.54	2	s	$-CH_2-$
3.80	3	s	methoxyl
3.85	2	s	benzylic CH_2
6.80 - 6.90	2	d(J=9Hz))	asymmetrical para
7.20 - 7.30	2	d(J=9Hz))	disubstituted benzene ring.

*disappeared after deuteration.

Mass spectrum

M^{+}. m/e 176 (4%); m/e 175 (3%); m/e 149 (3%); m/e 136 (4%); m/e 121 (100%).

2-(N-methyl-4-methoxybenzylamino)-2-spirocyclohexylacetonitrile(XXII)

Using 0.05 molar quantities.

Yield 9.2g (73%) as small colourless needles.

m.p. 88°

	C	H	N
Found	74.52	8.52	10.76%
$C_{16}H_{22}N_2O$ requires	74.41	8.53	10.85%

i.r. - C ≡ N 2240 cm^{-1}

n.m.r. (spectrum - page 137)

	int.	mult.	assignment
1.20 - 2.0	10	broad m.	cyclohexyl
2.20	3	s	$N-CH_3$
3.62	2	s	benzylic CH_2
3.81	3	s	methoxyl
6.85 - 6.95	2	d(J=9Hz))	asymmetrical para
7.20 - 7.30	2	d(J=9Hz))	disubstituted benzene ring

Mass Spectrum

M^+ m/e 258 (8%); m/e 231 (8%); m/e 216 (2%);

m/e 137 (4%); m/e 121 (100%).

m^* 201.9

2-(N-methyl-4-methoxybenzylamino)-2-spirocyclopentylacetonitrile(XXIII)

Using 0.05 molar quantities.

Yield 10.5g (82%) as fine colourless needles.

m.p. 73°

	C	H	N
Found	73.71	8.11	11.44%
$C_{15}H_{20}N_2O$ requires	73.77	8.13	11.38%

i.r. $-C \equiv N$ 2250 cm^{-1}

n.m.r.

δ	int.	mult.	assignment
1.65 - 2.10	8	m	cyclopentyl
2.15	3	s	$>N - CH_3$
3.55	2	s	benzylic - CH_2
3.75	3	s	methoxyl
6.80 - 6.95	2	d(J=9Hz))	asymmetrical para
		)	disubstituted
7.15 - 7.30	2	d(J=9Hz))	benzene ring.

Mass spectrum

M^+ m/e 244 (8%); m/e 217 (7%); m/4 202 (2%); m/e 121 (100%).

2-(N-methyl-4-methoxybenzylamino)-2-methylpropionitrile (XXIV)

Using 0.05 molar quantities.

Yield 9.8g (90%) as colourless needles.

m.p. 58°

	C	H	N
Found	71.60	8.40	12.60%
$C_{13}H_{18}N_2O$ requies	71.56	8.26	12.84%

i.r. - C ≡ N 2210 cm^{-1}

n.m.r.

δ	int.	mult.	assignment
1.60	6	s	2 x - CH_3
2.20	3	s	N - CH_3
3.60	2	s	benzylic CH_2
3.80	3	s	methoxyl
6.70 - 6.85	2	d(J=9Hz)	asymmetrical para disubstituted benzene ring
7.10 - 7.25	2	d(J=9Hz)	

Mass spectrum

M^+ m/e 218 (10%); m/e 191 (4%); m/e 176 (3%); m/e 121 (100%)

2-(N-benzyl-4-methoxybenzylamino)-2-spirocyclohexylacetonitrile(XXV)

Using 0.03 molar quantities.

Yield 6.2g (56%) as a viscous deep yellow thermolabile oil.

	C	H	N
Found	78.95	7.79	8.21%
$C_{22}H_{26}N_2O$ requires	79.04	7.78	8.38%

i.r. The expected - C ≡ N absorption at 2250 cm^{-1} was absent.

n.m.r.

δ	int.	mult.	assignment
1.40 - 2.0	10	m	cyclohexyl
3.70	2	s	2 x benzylic CH_2
3.73	2	s	

	int.	mult.	assignment
3.78	3	s	methoxyl
6.8 - 7.2	9	m	aromatic protons

Mass spectrum

$M^{+\cdot}$ m/e 334 (2%) ; m/e 307 (4%); m/e 216 (15%);
m/e 186 (10%); m/e 136 (20%); m/e 121 (100%);
m/e 106 (15%); m/e 91 (60%).

m^* 151.9

2-(N-veratryl-4-methoxybenzylamino)-2-~~spiro~~spiro cyclohexylacetonitrile

(XXVI)

Using 0.03 molar quantities.

Yield 5.1g (52%) as a pale brown, viscous, thermolabile (impure) oil.

Attempts to prepare the base hydrochloride failed.

i.r. - C ≡ N 2240 cm^{-1} (very weak).

n.m.r.

δ	int.	mult.	assignment
1.2 - 1.9	10	broad m	cyclohexyl
3.7 - 3.9	13	m	3 x methoxyl 2 x benzylic CH_2
6.8 - 7.4	7	m	aromatic protons

Mass spectrum

$M^{+\cdot}$ absent; m/e 287 (10%); m/e 257 (1%);
m/e 151 (30%); m/e 121 (100%).

2-[N-(4-chlorobenzyl)-4-methoxybenzylamino] -2-spirocyclohexyl-acetonitrile (XXVII)

Using 0.018 molar quantities.

Yield 4.5g (58%) as a pale brown, viscous thermolabile (impure) oil.

Attempts to prepare the base hydrochloride were unsuccessful.

i.r. $-C \equiv N$ 2250 cm^{-1} (very weak)

n.m.r.

δ	int.	mult.	assignment
1.2 - 2.0	10	m	cyclohexyl
3.68	2	s	methoxybenzylic CH_2
3.70	2	s	chlorobenzylic CH_2
3.76	3	s	methoxyl
6.8 - 6.9	2	d	part of AA'XX' of asymmetrical para disubstituted benzene ring.
7.1 - 7.6	6	m	remaining aromatic protons

Mass spectrum

$M^{+\cdot}$ m/e $368^{\dagger}$ (< 1%); m/e $341^{\dagger}$(1%); m/e $216^{\dagger}$ (36%); m/e $125^{\dagger}$ (45%); m/e 121 (100%).

($\dagger$ m + 2 ion also present)

2-[1-(4-methoxybenzyl)-2-phenethylamino] -2-spirocyclohexyl-acetonitrile. (XXVIII)

Using 0.05 molar quantities.

Yield 5.3g (67%) as white needles.

m.p. 121°

	C	H	N
Found	79.19	7.87	8.56%
$C_{22}H_{26}N_2O$ requires	79.04	7.78	8.38%

i.r. $-C \equiv N$ 2250 cm^{-1}

$>NH$ 3350 cm^{-1}

n.m.r. (spectrum - page 138)

δ	int.	mult.	assignment
1.0 - 1.8	11*	m	cyclohexyl + NH
2.79 - 2.91	2	m	benzylic CH_2
3.76	3	s	methoxyl
4.1 - 4.3	1		benzal CH
6.75 - 6.85	2	d(J=10Hz)	part of AA'XX' spin system.
7.0 - 7.3	7	m	aromatic protons

*reduced to 10 after deuteration

Mass Spectrum

M^+. m/e 334 (1%); m/e 307 (1%); m/e 243 (20%); m/e 216 (100%); m/e 211 (10%); m/e 186 (12%); m/e 172 (15%); m/e 121 (5%); m/e 91 (6%).

2-[N-(4-methoxybenzyl)-2-phenethylamino]-acetonitrile (XXIX)

Because of the low solubility in water of the amine hydrochloride this preparation was carried out on a boiling waterbath.

Using 0.05 molar quantities.

Yield 9.4g (67%) as a pale yellow, viscous, thermolabile oil.

The base hydrochloride (m.p. 202d) as white prisms was prepared for elemental analysis.

	C	H	N	Cl
Found	68.49	6.89	8.75	10.82%
$C_{18}H_{20}N_2O$ HCl requires	68.25	6.64	8.85	11.20%

i.r. (base) - C ≡ N 2220 cm^{-1}

n.m.r. (base)

δ	int.	mult.	assignment
2.80	4	s	$Ar-\underline{CH_2-CH_2}-N<$
3.45	2	s	$>N-\underline{CH_2}-CN$
3.60	2	s	$Ar-\underline{CH_2}-N$
3.80	3	s	methoxyl
6.80 - 6.90	2	d(J=10Hz)	part of AA'XX' spin system of methoxy benzyl.
7.1 - 7.4	7	m	aromatic protons

Mass spectrum (base)

$M^{+\cdot}$ m/e 280 (3%); m/e 240 (2%); m/e 189 (54%);

m/e 164 (18%); m/e 150 (18%); m/e 121 (100%).

m^* 127.6

2-[N-(4-methoxybenzyl)-homoveratrylamino] -acetonitrile (XXX)

Using 0.05 molar quantities.

Yield 6.0g (63%) as minute white prisms.

m.p. 62°

	C	H	N
Found	71.37	7.16	8.20%
$C_{20}H_{24}N_2O_3$ requires	70.59	7.06	8.24%

i.r. - C ≡ N 2230 cm^{-1}

n.m.r. (spectrum - page 139)

δ	int.	mult.	assignment
2.80	4	s	$Ar-CH_2-CH_2-N$
3.43	2	s	$N - CH_2 - C = N$
3.62	2	s	$Ar-CH_2-N$
3.60	3	s	1 x methoxyl
3.70	6	s	2 x methoxyl
6.65 - 6.77	3	m	aromatic protons of "dimethoxy ring"
6.80 - 6.90	2	d(J=9Hz))	asymmetrical para disubstituted benzene ring.
7.15 - 7.25	2	d(J=9Hz))	

Mass Spectrum

$M^{+\cdot}$ m/e 340 (18%); m/e 313 (0.5%); m/e 189 (30%);

m/e 165 (9%); m/e 151 (45%); m/e 121 (100%).

m^* 138.2

2-[N-(4-methoxybenzyl)-2-phenethylamino]-2-spirocyclohexyl-acetonitrile. (XXXI)

Using 0.1 molar quantities.

Yield 8.5g (24%) as small white prisms.

m.p. 128°

	C	H	N
Found	79.58	8.33	8.09%
$C_{23}H_{28}N_2O$ requires	79.31	8.05	8.05%

i.r. $-C \equiv N$ 2200 cm^{-1}

n.m.r.

δ	int.	mult.	assignment
1.4 - 2.1	10	broad m	cyclohexyl
2.6 - 3.0	4	m	$Ar-CH_2-CH_2-N<$
3.80	3	s	methoxyl
3.90	2	s	$Ar-CH_2-N<$
6.85 - 6.95	2	d(J=9Hz)	part of AA'XX' of asymmetrical para disubstituted benzene ring
7.10 - 7.4	7	m	aromatic protons

Mass Spectrum

M^+. absent; m/e 321 (10%); m/e 257 (4%); m/e 230 (30%); m/e 200 (3%); m/e 150 (6%); m/e 121 (100%); m/e 105 (8%); m/e 91 (10%).

m^* 164.8

2- N-(4-methoxybenzyl)-2-homoveratrylamino -2-spirocyclohexyl-acetonitrile (XXXII)

Using 0.005 molar quantities.

Yield 1.0g (48%) as white prisms.

m.p. 117°

	C	H	N
Found	72.94	7.80	6.94%
$C_{25}H_{32}N_2O_3$ requires	73.53	7.84	6.86%

i.r. $-C\equiv N$ 2250 (weak)

n.m.r.

δ	int.	mult.	assignment
1.5 - 2.10	10	broad m	cyclohexyl
2.75 - 2.85	4	t(J=4Hz)	$Ar-CH_2-CH_2-N<$
3.75 - 3.80	11	4 x s	$Ar-CH_2-N$
			+ 3 x methoxyl
6.40 - 7.24	7	m	aromatic protons

Mass spectrum

M^+ absent; m/e 381 (10%); m/e 301 (5%);
m/e 230 (70%); m/e 164 (40%); m/e 151(100%);
m/e 91 (25%).

2-benzyl-2-(4-methoxybenzylamino)-propionitrile (XXXIII)

Using 0.04 molar quantities.

Yield 9g (80%) as small white prisms.

m.p. 80°

	C	H	N
Found	76.90	7.20	9.68%
$C_{18}H_{20}N_2O$ requires	77.14	7.14	10.00%

i.r. $-C\equiv N$ 2250 cm^{-1}

$>NH$ 3320 cm^{-1}

n.m.r. (spectrum page 140)

δ	int.	mult.	assignment
1.34	3	s	$CH_3-\dot{C}-$
1.54	1*	s	$>NH$
2.89	2	s	$Ar-CH_2-\dot{C}-$
3.64	3	s	methoxyl

n.m.r. cont"d

δ	int.	mult.	assignment
3.76	2	s	$Ar-CH_2-N$
6.70 - 6.79	2	d(J=9Hz)	Part of AA'XX' of asymmetrical para disubstituted benzene ring.
7.08 - 7.30	7	m	aromatic protons

* disappeared on deuteration

Mass spectrum

$M^{+}\cdot$ m/e 280 (1%); m/e 253 (4%); m/e 190 (2%);

m/e 136 (22%); m/e 121 (100%); m/e 91 (6%);

m^{*} 32.0

2-veratryl-2-(4-methoxybenzylamino)-propiontrile (XXXIV)

Using 0.05 molar quantities.

Yield 13g (75%) as a yellow thermolabile semi solid.

Attempts to prepare the base hydrochloride were unsuccessful.

i.r. - CN 2240 cm^{-1}

$>NH$ 3350 cm^{-1}

n.m.r.

δ	int.	mult.	assignment
1.45	3	s	$CH_3-\dot{C}-$
2.25	1*	s	$>NH$
2.90	2	s	$Ar-CH_2-\dot{C}-$
3.80	2	s	$Ar-CH_2-N<$
3.84	3	s	1 x methoxyl
3.87	6	s	2 x methoxyl
6.75 - 7.35	7	s	aromatic protons

* disappeared on deuteration

Mass spectrum

$M^{+\cdot}$ m/e 340 (<1%); m/e 313 (30%); m/e 272 (5%);

m/e 192 (4%); m/e 162 (3%); m/e 151 (50%);

m/e 121 (100%).

2-(4-chlorobenzyl)-2-(4-methoxybenzylamino)-propionitrile (XXXV)

Using 0.1 molar quantities.

Yield 15g (48%) as a yellow oil which crystallised after several weeks as large colourless prisms.

m.p. 72°

	C	H	N	Cl
Found	68.23	6.04	8.53	10.80%
$C_{18}H_{19}N_2O$ Cl requires	68.68	6.04	8.90	11.29%

i.r.

$-C\equiv N$	2250 cm^{-1}	
$>NH$	3340 cm^{-1}	

n.m.r.

δ	int.	mult.	assignment
1.40	4*	s	$CH_3-\overset{|}{C}-$ + $>NH$
2.95	2	s	$Ar-CH_2-\overset{|}{C}-$
3.76	3	s	methoxyl
3.84	2	s	$Ar-CH_2-N<$
6.84 - 6.94	2	d	part of AA'XX' of asymmetrical para disubstituted benzene ring
7.18 - 7.4	6	m	aromatic protons

* reduced to 3 after deuteration.

Mass spectrum

M^{+} m/e 314† (1%); m/e 287† (10%); m/e 189 (5%);

m/e 162 (10%); m/e 125† (90%); m/e 121 (100%).

(† m + 2 ion also present)

2-(4-methoxybenzylamino)-4-(3,4-dimethoxyphenyl)-2-methyl-butyronitrile (XXXVI)

Using 0.1 molar quantities.

Yield 19g (65%) as a pale brown semi solid.

	C	H	N
Found	71.38	7.47	8.08%
$C_{21}H_{26}N_2O_3$ requires	71.19	7.34	7.91%

i.r. $-C\equiv N$ 2250 cm^{-1}

$>NH$ 3300 cm^{-1}

n.m.r. (Spectrum page 141)

δ	int.	mult.	assignment
1.42	1*	s	$>NH$
1.48	3	s	$CH_3-\dot{C}-$
2.0	2	m	$Ar-\underline{CH_2}-CH_2-$
2.7	2	m	$Ar-CH_2-\underline{CH_2}-$
3.6 - 3.84	11	m	3 x methoxyl + benzylic $CH_2-N<$
6.6 - 7.30	7	m	aromatic protons

* disappeared on deuteration

Mass spectrum

M^{+} m/e 354 (< 1%); m/e 327 (26%); m/e 206 (16%);

m/e 190 (10%); m/e 176 (30%); m/e 164 (70%);

m/e 151 (80%); m/e 136 (30%); m/e 121 (100%).

2-(4-methoxybenzylamino)-2-methyl-4-phenylbutyronitirile (XXXVII)

Using 0.1 molar quantities.

Yield 19.0g (65%) as a viscous thermolabile yellow oil.

The base hydrochloride (fine white prisms, m.p.220° d) was prepared for elemental analysis.

	C	H	N	Cl
Found	69.07	6.86	8.27	10.41%
$C_{19}H_{22}N_2O.HCl$ requires	68.99	6.96	8.47	10.74%

i.r. (base) $-C \equiv N$ 2220 cm^{-1}

$>NH$ 3350 cm^{-1}

n.m.r. (base)

δ	int.	mult.	assignment
1.47	3	s	$CH_3-\overset{|}{C}-$
1.50 - 1.65	1*	broad s	$>NH$
1.70 - 2.15	2	m	$Ar-CH_2-CH_2-\overset{\|}{C}-$
2.62 - 2.95	2	m	$Ar-CH_2-CH_2-\overset{\|}{C}-$
3.72	3	s	methoxyl
3.80	2	s	$Ar-CH_2-N$
6.75 - 7.30	9	m	aromatic protons

* disappeared on deuteration

Mass spectrum

$M^{+\cdot}$ m/e 294 (2%); m/e 267 (35%); m/e 121 (100%); m/e 105 (10%); m/e 91 (22%).

2-(4-dimethylaminobenzylamino)-2-spirocyclohexylacetonitrile

(XXXVIII)

Using 0.1 molar quantities.

Yield 18.4g (72%) as pale yellow needles.

m.p. 72°

	C	H	N
Found	75.36	8.84	15.61%
$C_{16}H_{23}N_3$ requires	74.70	8.90	16.30%

i.r.

- C ≡ N	2250 cm^{-1}	
>NH	3310 cm^{-1}	

n.m.r.

δ	int.	mult.	assignment
1.1 - 2.2.	11*	m	cyclohexyl + >NH
2.90	6	s	2 x CH_3 -
3.78	2	s	benzylic CH_2
6.64 - 6.73	2	d)	asymmetrical para
		)	disubstituted
7.17 - 7.26	2	d)	benzene ring.
7.40	- impurity		

* reduced to 10 after deuteration.

Mass spectrum

M^+. m/e 257 (4%); m/e 230 (12%); m/e 134 (100%).

2-(3,4,5-trimethoxybenzylamino)-2-spirocyclohexylacetonitrile (XIL)

Previously reported [49].

General method for attempted cyclisation of substituted benzylaminonitriles

The aminonitrile (5g) was added carefully to cold concentrated sulphuric acid (25 ml) in an ice bath, stirring continuously until solution was complete. The solution was allowed to stand at room temperature for approximately 18 hours (referred to as COLD CYCLISATION) or alternatively heated to 50°C for 4 hours (referred to as HOT CYCLISATION), diluted by pouring on to crushed ice and allowed to stand for 30 minutes. Aqueous 5N sodium hydroxide was used to basify the diluted mixture, ice being added from time to time to prevent a rise in temperature. The product was either filtered off (when solid) or extracted with chloroform (when an oil), washed, dried and recrystallised from petrcleum ether (b.p. 80-100°).

Where the product was a liquid, the hydrochloride was precipitated by passing dry HCl gas into an ethereal solution of the base and the product recrystallised from alcohol ether mixture (1:1).

Attempted cyclisation of:

2-(4-dimethylaminobenzylamino)-2-spirocyclohexylacetonitrile (XXXVIII)

Both hot and cold methods of treatment gave 2-(4-dimethylaminobenzylamino)-2-spirocyclohexylacetamide as pale yellow needles.

Yield 4.5g (90%)

m.p. 133°

	C	H	N
Found	69.93	9.31	15.34%
$C_{16}H_{25}N_3O$ requires	69.80	9.10	15.30%

i.r.

>CO	1660 cm^{-1}	(amide I)
>NH	1610 cm^{-1}	(amide II)
>NH (amine + amide)	(3350 cm^{-1} (3100 cm^{-1}	

n.m.r.

δ	int.	mult.	assignment.
1.20 - 2.0	11**	m	cyclohexyl + NH
2.92	6	s	$N(CH_3)_2$
3.50	2	s	benzylic-CH_2-N
5.8 - 6.1	1*	broad s	NH(amide)
6.66 - 7.74	2	d(J=8Hz))	asymmetrical para
7.15 - 7.23	2	d(J=8Hz))	disubstituted benzene ring
7.2 - 7.5	1*	broad s	NH(amide)

* reduced to 10 after deuteration

** reduced after deuteration indicating slow exchange.

Mass spectrum

M^+ m/e 275 (25%); m/e 231 (35%); m/e 149 (100%);

m/e 134 (80%); m/e 44 (5%).

m^* 194.0, 80.7, 77.7.

Cyclisation of 2-(3,4,5-trimethoxybenzylamino)-2-spirocyclohexyl-acetonitrile (XIL)

a) cold cyclisation using 5g (0.016M)

The dried chloroform extract gave on evaporation an oil (1.6g) which, after refluxing with petroleum ether

(b.p. 40-60°) yielded the amide as small white prisms. (L; 375 mg; 7% m.p. 154°). Concentration of the petroleum ether solution yielded a second crop of crystals as white prisms which were shown to be the trimethoxyisoquinolinone (XLIX; 1.1g, 22%; m.p. 128°).

Acidification of the extracted aqueous solution gave no precipitate.

b) hot cyclisation using 5g (0.016M).

The dried chloroform extract, on evaporation and recrystallisation from petroleum ether (b.p. 40-60°) gave the amide (L; 320 mg; 6%; m.p. 154°) and the trimethoxyisoquinolinone (XLIX; 360 mg; 6%; m.p. 128°).

The extracted aqueous solution was then made strongly acid with hydrochloric acid giving a copious white precipitate (1.4g), which was collected and suspended in water (100 ml), and an excess of sodium bicarbonate added. The reaction mixture was extracted with three 40 ml. portions of chloroform, the combined chloroform extracts washed once with water (10 ml), dried ($MgSO_4$) and the chloroform removed. Recrystallisation from petroleum ether gave the hydroxydimethoxyisoquinolinone as small white prisms (L1; 1.0g; 20%; m.p. 149°).

2-(2,3,4-trimethoxybenzylamino)-2-spirocyclohexylacetamide (L)

	C	H	N
Found	63.70	8.17	8.51%
$C_{17}H_{26}N_2O_4$ requires	63.35	8.07	8.70%

i.r.

- NH_2 (amide)	3200 cm^{-1}
	3450 cm^{-1}
- NH (amine)	3320 cm^{-1}
- CO (amide)	1660 cm^{-1}

n.m.r. (spectrum page 142)

δ	int.	mult.	assignment.
1.2 - 2.0	11*	m	cyclohexyl + NH
3.56	2	s	benzylic CH_2
3.84 - 3.88	9	2 x s	3 x methoxyl
6.14	1**	broad s	NH(amide)
6.56	2	s	aromatic protons
7.17	1**	broad s	NH(amide)

* reduced to 10 after deuteration

** reduced integral after deuteration indicating slow exchange.

Mass spectrum

M^+ m/e 322 (< 1%); m/e 278 (90%); m/e 196 (50%); m/e 181 (100%).

1.2 dihydro-5,6,7-trimethoxy-3-spirocyclohexylisoquinolin-4(3H)-one

(XLIX)

		C	H	N
Found		66.54	7.20	4.60%
$C_{17}H_{23}NO_4$ requires		66.80	7.54	4.58%
i.r.	>NH		3290 cm^{-1}	
	>CO		1650 cm^{-1}	

n.m.r. (spectrum page 143)

δ	int.	mult.	assignment.
1.4 - 1.8	10	m	cyclohexyl
1.85	1*	s	>NH
3.84	3	s	3 x methoxyl
3.90	6	s	

n.m.r. cont'd

δ	int.	mult.	assignment.
4.0	2	s	benzylic CH_2
6.38	1	s	aromatic proton

* disappeared after deuteration.

Mass spectrum

M^+ m/e 305 (31%); m/e 303 (10%); m/e 288 (5%);
m/e 277 (3%); m/e 234 (3%); m/e 208 (100%);
m/e 193 (20%); m/e 181 (72%); m/e 165 (20%).

1,2-dihydro-7-hydroxy-6,8-dimethoxy-3-spirocyclohexylisoquinolin-4(3H)-one (LI)

		C	H	N
Found		66.20	7.33	4.74%
$C_{16}H_{21}NO_4$	requires	65.98%	7.22%	4.81%

i.r.

- OH	3450 cm^{-1}
> NH	3350 cm^{-1}
= CO	1660 cm^{-1}

n.m.r. (spectrum page 144)

δ	int.	mult.	assignment.
1.5 - 1.8	10	broad s	cyclohexyl
3.88) 3.90)	6	2 x s	2 x methoxyl
4.06	4*	s (with "shoulder")	benzylic CH_2 + -OH + >NH
7.34	1	s	aromatic proton

* reduced to 2 after deuteration

Mass spectrum

$M^{+\cdot}$ m/e 291 (40%); m/e 290 (5%); m/e 263 (4%);
m/e 248 (4%); m/e 232 (40%); m/e 220 (20%);
m/e 194 (16%); m/e 167 (100%); m/e 145.5 (10%).

Attempted dehydroxylation[101] of 1,2-dihydro-7-hydroxy-6,8-dimethoxy-3-spirocyclohexylisoquinolin-4(3H)-one. (LI)

Pyridine (0.25 ml, 3.5×10^{-3} mol) and carbon disulphide (2 ml) were mixed and cooled to ca. -10°. Chlorosulphuric acid (0.13 ml, 2×10^{-3} mol) was added and after five minutes the hydroxy compound (LI, 200 mg, 0.7×10^{-3} mol) was added and the mixture stirred for 1 hour at room temperature. The carbon disulphide was allowed to evaporate and a solution of potassium hydroxide (0.25g) in water (5 ml) was added.

No attempt was made to isolate the potassium salt.

The reaction mixture was added to a stirred suspension of nickel-aluminium alloy (1g) in sodium hydroxide (20 ml 2.5N) solution and the stirring continued for 1 hour. The nickel was removed by filtration and the filtrate extracted with 3 x 10 ml chloroform. Drying ($Mg SO_4$) and removal of the chloroform gave only a trace of residue ($< 1mg$).

Attempted oxidation of 1,2-dihydro-7-hydroxy-6,8-dimethoxy-3-spirocyclohexylisoquinolin-4(3H)-one (LI)

The isoquinolinone (LI, 200 mg) was refluxed with N-bromosuccinimide (125 mg) in carbon tetrachloride (25 ml) for 4 hours, until all the solid had risen to the surface. The

solid was filtered off and the solvent removed under reduced pressure, leaving a small quantity of acid insoluble brown gum. This experiment was abandoned.

4-(4-methoxyphenyl)-5-spirocyclopentyl -3-imidazoline (LV)

Prepared from XVI by cold cyclisation.

Yield 2.6g (64%) as large colourless oblong crystals

m.p. 90°

	C	H	N
Found	73.20	7.98	11.89%
$C_{14}H_{18}N_2O$ requires	73.06	7.81	12.17%

i.r. >NH 3380 cm^{-1}

n.m.r.

δ	int.	mult.	assignment.
1.60 - 2.30	9*	m	cyclopentyl + >NH
3.82	3	s	methoxyl
4.72	2	s	= N-CH_2-N<
6.82 - 6.98	2	d(J=9Hz))	asymmetrical para disubstituted
7.68 - 7.82	2	d(J=9Hz))	benzene ring

* reduced to 8 after deuteration

Mass spectrum

M^+ m/e 230 (4%); m/e 229 (12%); m/e 228 (2%); m/e 202 (40%); m/e 201 (50%); m/e 147 (16%); m/e 133 (10%); m/e 97 (94%); m/e 96 (100%).

5, 5-diethyl-4-(4-methoxyphenyl)-3-imidazoline (LVI)

Prepared from XVII by cold cyclisation.

Yield 4g (80%) as a viscous oil.

The base hydrochloride as small white prisms (m.p. 158° d) was prepared for elemental analysis.

	C	H	N	Cl
Found	62.55	7.80	10.20	13.20%
$C_{14}H_{20}N_2O$ HCl requires	62.57	7.82	10.42	13.22%

i.r. (base) >NH 3350 cm^{-1}

n.m.r. (base) (spectrum page 145)

δ	int.	mult.	assignment.
0.78 - 0.96	6	t	2 x $-CH_3$ (of ethyl groups)
1.64 - 2.08	4	m	2 x $-CH_2-$ (of ethyl groups)
2.14	1*	s	>NH
3.72	3	s	methoxyl
4.86	2	s	$=N-CH_2-N<$
6.84 - 6.98	2	d(J=9Hz))	asymmetrical para
7.78 - 7.70	2	d(J=9Hz))	disubstituted benzene ring.

* disappeared on deuteration.

Mass spectrum (base)

M^+ m/e 232 (6%); m/e 231 (3%); m/e 230 (3%);
m/e 204 (30%); m/e 203 (100%); m/e 147 (6%);
m/e 133 (8%); m/e 99 (70%); m/e 98 (12%);
m/e 97 (20%).

m^* 174.2

5-ethyl-5-methyl-4-(4-methoxyphenyl)-3-imidazoline (LVII)

Prepared from XVIII by cold cyclisation.

Yield 4.3g (87%) as a viscous oil.

The base hydrochloride, as white prisms (m.p. 160°d) was prepared for elemental analysis.

	C	H	N	Cl
Found	61.30	7.75	9.53	13.85%
$C_{13}H_{18}N_2O.HCl$ requires	61.30	7.47	11.0	13.95%

i.r. (base) >NH 3320 cm^{-1}

n.m.r. (base) (spectrum page 146)

δ	int.	mult.	assignment.
0.80 - 0.98	3	t	CH_3 (of ethyl group)
1.48	3	s	CH_3-
1.72 - 2.00	2	q	CH_2 (of ethyl group)
2.30	1*	s	NH
3.84	3	s	methoxyl
4.80	2	s	= N-CH_2-N
6.84 - 6.98	2	d(J=9Hz)	) asymmetrical para
7.72 - 7.88	2	d(J=9Hz)	) disubstituted benzene ring.

* disappears after deuteration.

Mass spectrum

M^+ m/e 218 (8%); m/e 217 (4%): m/e 216 (4%):
m/e 203 (10%); m/e 189 (80%): m/e 174 (8%);
m/e 147 (4%); m/e 133 (5%); m/e 85 (100%);
m/e 84 (10%); m/e 83 (10%).

m^* 33.14; 36.8.

5,5-dimethyl-4-(4-methoxyphenyl)-3-imidazoline (LVIII)

Prepared from XIX by cold cyclisation.

Yield 2.4g (47%) as colourless prisms.

m.p. 64°

	C	H	N
Found	70.40	7.72	13.72%
$C_{12}H_{16}N_2O$ requires	70.60	7.85	13.73%

i.r. $>NH$ 3350 cm^{-1}

n.m.r. (spectrum page 147)

δ	int.	mult.	assignment.
1.48	6	s	2 x CH_3-C
2.04	1*	s	$>NH$
3.82	3	s	methoxyl
4.80	2	s	= N-CH_2-N<
6.84 - 7.00	2	d(J=9Hz)	asymmetrical para disubstituted benzene ring.
7.70 - 7.84	2	d(J-9Hz)	

* disappeared on deuteration.

Mass spectrum

M^+ m/e 204 (5%); m/e 189(17%); m/e 147 (4%):
m/e 133 (4%); m/e 71 (100%).

m^* 25.0

1-methyl-4-(4-methoxyphenyl)-5-spirocyclohexyl-3-imidazoline(LIX)

Prepared from XXII by cold cyclisation.

Yield 4.8g (96%) as white needles.

m.p. 97°

	C	H	N
Found	74.60	8.70	10.72%
$C_{16}H_{22}N_2O$ requires	74.42	8.53	10.85%

n.m.r.

δ	int.	mult.	assignment.
1.5 - 2.2	10	m	cyclohexyl
2.35	3	s	$\rangle$N -Me
3.85	3	s	methoxyl
4.60	2	s	= N-CH_2-N$\langle$
6.80 - 7.00	2	d(J=9Hz))	asymmetrical para
7.50 - 7.70	2	d(J=9Hz))	disubstituted benzene ring.

Mass spectrum

M^+ m/e 258 (22%); m/e 243 (2%); m/e 215 (100%); m/e 202 (20%); m/e 147 (8%); m/e 133 (10%); m/e 125 (100%); m/e 97 (22%).

97 (22%). m^* 60.56, 179.2.

1-methyl-4-(4-methoxyphenyl)-5-spirocyclopentyl-3-imidazoline(LX)

Prepared from XXIII by cold cyclisation.

Yield 4.6g (92%) as white needles.

m.p. 89°

	C	H	N
Found	73.81	8.30	11.16%
$C_{15}H_{20}N_2O$ requires	73.77	8.19	11.47%

n.m.r.

δ	int.	mult.	assignment.
1.7 - 2.1	8	m	cyclopentyl
2.40	3	s	$>N - Me$
3.80	3	s	methoxyl
4.58	2	s	$= N-CH_2-N<$
6.88 -6.96	2	d(J=8Hz))	asymmetrical para
		)	disubstituted
7.72 -7.80	2	d(J=8Hz))	benzene ring

Mass spectrum

$M^{+\cdot}$ m/e 244 (16%); m/e 215 (50%); m/e 147 (8%);

m/e 133 (8%); m/e 111 (100%).

1,5,5-trimethyl-4-(methoxyphenyl)-3-imidazoline (LXI)

Prepared from XXIV by cold cyclisation.

Yield 0.5g (10%) as fine white needles.

m.p. 60°

	73	H	N
Found	71.40	8.32	12.84%
$C_{13}H_{18}N_2O$ requires	71.56	8.26	12.84%

n.m.r.

δ	int.	mult.	assignment.
1.12	6	s	$2 \times -CH_3$
2.30	3	s	$>N - CH_3$
3.84	3	s	methoxyl
4.68	2	s	$= N-CH_2-N<$
6.92 - 7.00	2	d(J=8Hz))	asymmetrical para
		)	disubstituted
7.60 - 7.68	2	d(J=8Hz))	benzene ring.

Mass spectrum

$M^{+\cdot}$ m/e 218 (8%); m/e 203 (100%); m/e 188 (14%);
m/e 85 (100%); m/e 70 (24%).

1-benzyl-4-(4-methoxyphenyl)-5-spirocyclohexyl-3-imidazoline (LXII)

Prepared from XXV by cold cyclisation.

Yield 3.2g (64%) as white needles.

m.p. 128°

	C	H	N
Found	78.91	7.83	8.38%
$C_{22}H_{26}N_2O$ requires	79.04	7.78	8.38%

n.m.r. (spectrum page 148)

δ	int.	mult.	assignment.
1.4 - 2.1	10	m	cyclohexyl
3.68	2	s	Ar-CH_2-N<
3.82	3	s	methoxyl
4.52	2	s	=N-CH_2-N<
6.90 - 6.98	2	d(J=8Hz))	asymmetrical para
7.68 - 7.76	2	d(J=8Hz))	disubstituted benzene ring.
7.24 - 7.60	5	m	C_6H_5 -

Mass spectrum

$M^{+\cdot}$ m/e 334 (30%); m/e 291 (90%); m/e 278 (14%);
m/e 243 (10%); m/e 201 (100%); m/e 187 (20%);
m/e 147 (10%); m/e 110 (60%); m/e 91 (90%).

m^* 253.5

1-(4-chlorobenzyl)-4-(4-methoxyphenyl)-5-spirocyclohexyl-3-imidazoline (LXIII)

Prepared from XXVII by cold cyclisation.

Yield 0.5g (10%) as a yellow oil.

Attempts to purify this compound by formation of the hydrochloride were unsuccessful.

n.m.r.

δ	int.	mult.	assignment.
1.2 - 2.0	10	m	cyclohexyl
3.64	2	s	Ar-CH_2-N
3.86	3	s	methoxyl
4.50	2	s	= N-CH_2-N
6.90 - 7.70	8	m	aromatic protons

Mass spectrum

$M^{+\cdot}$ m/e 368† (12%); m/e 326† (30%); m/e 325† (40%); m/e 243 (10%); m/e 235† (80%); m/e 201 (14%); m/e 187 (10%); m/e 125† (80%); m/e 110 (100%).

(† m + 2 peak also present.)

m^* 287.0, 160.4

2-benzyl-4-(4-methoxyphenyl)-5-spirocyclohexyl-3-imidazoline (LXIV)

Prepared from XXVIII by cold cyclisation.

In this preparation the acid solution was basified with sodium bicarbonate.

Yield 3.8g (76%) as long white needles.

m.p. 95°

	C	H	N
Found	78.94	7.96	8.15%
$C_{22}H_{26}N_2O$ requires	79.04	7.78	8.38%

i.r. >NH 3350 cm^{-1}

n.m.r. (spectrum page 149)

δ	int.	mult.	assignment.
1.0 - 1.9	11*	m	cyclohexyl + NH
3.10 - 3.16	2	d(J=5Hz)	$Ar-CH_2-C$
3.80	3	s	methoxyl
5.14 -5.24	1	t(J=5Hz)	= N-CH-N<
6.84 - 7.92	2	d(J=9Hz))	asymmetrical para
7.64 - 7.74	2	d(J=9Hz))	disubstituted benzene ring
7.28	5	s	C_6H_5 -

* reduced to 10 after deuteration.

Mass spectrum

M^+ m/e 334 (2%); m/e 243 (100%); m/e 187 (2%); m/e 160 (2%); m/e 91 (12%).

m^* 143.9, 136.9

Attempted preparation of

1-veratryl-4-(4-methoxyphenyl)-5-spirocyclohexyl-3-imidazoline

The nitrile XXVI was ~~heated~~ treated with concentrated sulphuric acid at room temperature as described. No identifiable product could be isolated after the usual work up procedure. This experiment was abandoned.

5-methyl-4-(4-methoxyphenyl)-3-imidazoline (LXVI)

Prepared from XX by cold cyclisation.

The diluted reaction mixture was a deep purple colour, changing to green on basification. The chloroform extract was green, changing to red-brown on standing in air.

Drying ($MgSO_4$) and removal of the chloroform gave a brown resin which was refluxed with petroleum ether (100 ml b.p. 60-80°). The hot petroleum ether was filtered and allowed to cool giving an opaque yellow oil (1.6g), which t.l.c. showed to be a mixture.

Column chromatography on a 20 cm x 2 cm column of Brockmann Grade 1 neutral alumina was used in an attempt to separate the constituents. The oil (0.5g) was introduced on to the column in chloroform solution and eluted at a solvent rate of 5-8ml per minute, the eluent collected in 50 ml portions and the solvent removed under reduced pressure.

The composition of the eluent was varied as follows:-

	Pet.ether (b.p.60 - 80°)	Ethyl Acetate
Fractions - 1 - 10	70	30
11 - 16	50	50
17 - 24		100

The fractions giving significant amounts of residue after removal of the solvent were:

Fraction 1	200 mg
Fraction 4	140 mg
Fraction 24	150 mg

Each fraction was analysed spectroscopically but this was not conclusive and elemental analysis was not carried out.

Fraction 1

(reported as 2,5-di(4-methoxyphenyl)-3,6-dimethylpyrazine LXV)

i.r. para disubstituted benzene ring 850 cm^{-1}

Absence of absorption at 2250 cm^{-1} (C ≡ N absent)

1600 - 1800 cm^{-1} (>CO absent)

3000 cm^{-1} (>NH,-OH absent)

n.m.r. (spectrum page 150)

δ	int.	mult.	assignment.
2.63	6	s	2 x CH_3 -
3.86	6	s	2 x methoxyl
6.96 - 7.04	4	d(J=8Hz)	asymmetrical para disubstituted benzene ring.
7.54 - 7.62	4	d(J=8Hz)	

Mass spectrum

M^{+} m/e 320 (100%); m/e 160 (15%).

m^{*} 80.0

Fraction 2.

i.r. para disubstituted benzene ring 850 cm^{-1}

>CO 1680 cm^{-1}

broad band with a central peak 3000 - 3700 cm^{-1}

(-OH + NH)?

n.m.r.

δ	int.	mult.	assignment.
2.20 - 2.40	1	broad s	NH or - OH
2.60	3	s	- CH_3
3.86	3	s	methoxyl

n.m.r. cont'd

	int.	mult.		assignment.
6.96 - 7.04	2	d(J=8Hz)	)	asymmetrical para
			)	disubstituted
7.55 - 7.63	2	d(J=8Hz)	)	benzene ring.

Mass spectrum

M^+ m/e 243 (1%); m/e 203 (10%); m/e 189 (10%);

m/e 135 (40%); m/e 133 (80%); m/e 105 (70%);

m/e 91 (100%).

Fraction 24 (reported as imidazoline LXVI)

m.p. 60°

i.r. >NH 3350 cm^{-1}

n.m.r.

δ	int.	mult.	assignment.
1.30	3	d	$-CH_3$
3.20	1*	broad s	NH
3.84	3	s	methoxyl
4.1	1	m	>CH - Me
4.90	2	m	$=N-CH_2-N<$
6.88 - 6.96	2	d(J=8Hz))	asymmetrical para
		)	disubstituted
7.70 - 7.78	2	d(J=8Hz))	benzene ring.

* disappeared on deuteration

Mass spectrum

M^+ m/e 190 (25%); m/e 175 (20%): m/e 147(10%);

m/e 133 (14%); m/e 57 (100%).

2-(4-methoxybenzoylmethyl)-1,2,3,4-tetrahydroisoquinoline (LXVII)

Prepared from XXIX by hot cyclisation.

Yield approx. 5 mg (0.1%)

Mass spectrum

$M^{+\cdot}$ m/e 281 (8%); m/e 146 (27%); m/e 132 (27%);

m/e 117 (100%); m/e 115 (45%).

2-(4-methoxybenzoylmethyl) -6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (LXVIII)

Prepared from XXX by hot cyclisation.

Yield 1.7g (33%) as pale yellow needles.

	C	H	N
Found	70.52	6.68	4.08%
$C_{20}H_{23}NO_4$ requires	70.38	6.74	4.11%

i.r. $>C=O$ 1675 cm^{-1}

n.m.r. (spectrum page 151)

δ	int.	mult.	assignment.
2.74	4	s	$Ar-CH_2-CH_2-N<$ (of heterocycle)
3.70	2	s	$Ar-CH_2-N<$ (of heterocycle)
3.79 - 3.82	9	3 x s	3 x methoxyl
3.88	2	s	$-\overset{O}{\overset{\|}{C}} - CH_2 - N<$
6.47	1	s	aromatic protons of heterocycle
6.56	1	s	
6.84 - 6.93	2	d(J=8Hz)	asymmetrical para disubstituted benzene ring.
8.00 - 8.08	2	d(J=8Hz)	

Mass spectrum

M^{+} m/e 341 (6%); m/e 206 (100%); m/e 192 (60%);
m/e 135 (26%); m/e 107 (12%).

m^{*} 108.1, 84.8.

Attempted cyclisation of
2-[N-(4-methoxybenzyl)-2-phenethylamino]-2-spirocyclohexyl-acetonitrile (XXXI)

By 1) cold cyclisation using 3.5g (0.01 mol) nitrile
2) hot cyclisation using 3.5g (0.01 mol) nitrile.

Neither method of cyclisation gave an identifiable product and this experiment was abandoned.

Attempted cyclisation of
2-[N-(4-methoxybenzyl)-2-homoveratrylamino]-2-spirocyclohexyl-acetonitrile (XXXII)

Prepared from 1.0g (XXXII) by cold cyclisation.

Yield 200 mg of white amorphous solid.

m.p. 185° d.

The precipitate obtained on basification of the diluted sulphuric acid solution was extracted with chloroform. Drying ($Mg SO_4$) and removal of the chloroform gave a yellow gum (700 mg) which was insoluble in boiling petroleum ether (b.p. 60-80°). Re-crystallisation from ethylacetate/petroleum ether mixture 1:1 gave an amorphous white solid (200 mg).

i.r. para disubstituted benzene ring 840 cm^{-1}

OH 3000 - 3750 cm^{-1}

The n.m.r. spectrum was unsatisfactory, all signals being recorded as very broad singlets and suggesting a polymeric structure.

Mass spectrum

M^{+}? m/e 502 (2%); m/e 392 (4%); m/e 378 (4%); m/e 258 (50%); m/e 215 (30%); m/e 201 (80%); m/e 150 (100%); m/e 136 (38%); m/4 121 (40%).

3-(4-methoxybenzoyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline (LXIX)

Prepared from XXXIII by cold cyclisation.

Yield 3.6g (73%) as white needles.

m.p. 125°

	C	H	N
Found	76.84	6.74	4.78%
$C_{18}H_{19}NO_2$ requires	76.87	6.76	4.98%

i.r. C = O 1660 cm^{-1}

NH 3400 cm^{-1}

n.m.r. (spectrum page 152)

δ	int.	mult.	assignment.
1.55	3	s	CH_3-
1.90	1*	s	NH
2.56 - 2.75	1	d(J=16Hz)	Ar-CH_2-C
3.44 - 3.60	1	d(J=16Hz)	(AB quartet)

δ A = 3.50 ppm

δ B = 2.66 ppm

n.m.r. cont'd

δ	int.	mult.	assignment.
3.82	3	s	methoxyl
3.91 - 3.94	2	d(J=3Hz) (centre lines of AB quartet)	$Ar-CH_2-N<$
6.80 - 6.90	2	d(J=10Hz)	asymmetrical para disubstituted benzene ring.
8.28 - 8.38	2	d(J=10Hz)	
6.90 - 7.20	4	m	Aryl protons of heterocycle.

* disappeared on deuteration

Mass spectrum

$(M + 1)^+$ m/e 282 (4%); M^+ m/e 281(2%); m/4 280 (1%);
m/e 279 (1%); m/e 146 (100%); m/e 144 (50%);
m/e 135 (60%); m/e 107 (12%); m/e 77 (50%).
m^* 142.0

3-(4-methoxybenzoyl)-6, 7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (LXX)

Prepared from XXIV by cold cyclisation.

Yield 1.5g (30%) as white needles.

m.p.

	C	H	N
Found	70.52	6.78	4.31%
$C_{20}H_{23}NO_4$ requires	70.38	6.74	4.10%

i.r. >C = O 1660 cm^{-1}

>NH 3400 cm^{-1}

n.m.r.

δ	int.	mult.		assignment.
1.50	3	s		CH_3-
1.74	1*	s		>NH
2.40 - 2.67	1	d(J=16Hz)	)	Ar-CH_2-C
			)	AB quartet
3.28 - 3.55	1	d(J=16Hz)	)	δ A = 3.39 ppm
				δ B = 2.55 ppm
3.74	2	s		Ar-CH_2-N<
3.79	9	s		3 x methoxyl
6.40	1	s	)	aryl protons
			)	
6.56	1	s	)	of heterocycle
6.77 - 6.92	2	d(J=8Hz)	)	asymmetrical para
			)	disubstituted
8.25 - 8.50	2	d(J=8Hz)	)	benzene ring.

* NOT removed or reduced by deuteration

Mass spectrum

M^+ m/e 341 (<1%); m/e 206 (100%); m/e 190 (3%);

m/e 135 (5%): m/e 107 (2%); m/e 77 (20%).

Attempted cyclisation of

2-(4-chlorobenzyl)-2-(4-methoxybenzylamino)-propionitrile (XXXV)

1. By "cold cyclisation".

2. By "hot cyclisation".

With both methods the diluted reaction mixture was a green colour which rapidly changed to purple. Extraction with chloroform gave a brown amorphous material which was not identified.

7,8-dimethoxy-3-(4-methoxybenzoyl)-3-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine (LXXIV)

Prepared from XXXVI by cold cyclisation.

Yield 2.5g (50%) as fine white needles.

m.p. 116°

	C	H	N
Found	71.41	7.10	3.71%
$C_{21}H_{25}NO_4$ requires	70.99	7.40	3.90%

i.r. >C = O 1665 cm^{-1}

>NH 3400 cm^{-1}

n.m.r. (spectrum page 153)

δ	int.	mult.	assignment.
1.42	3	s	CH_3
1.50 - 1.61	2*	d	NH + 1H of $-CH_2 - CH_2 -$
2.60 - 3.0	3	m	3H of - CH_2-CH_2-
3.63	2	s	Ar-CH_2-N
3.80 - 3.85	9	3 x s	3 x methoxyl
6.56	1	s	aromatic protons of heteocycle.
6.70	1	s	
6.88 - 6.96	2	d(J=9Hz)	asymmetrical para disubstituted benzene ring.
8.24 - 8.32	2	d(J=9Hz)	

* reduced after deuteration

Irradiation of the multiplet (2.60 - 3.0 ppm) reduced the doublet at 1.50 - 1.61 ppm to a singlet.

Irradiation of the doublet (1.50 - 1.61 ppm) simplified the multiplet at 2.60 - 3.0 ppm.

Mass spectrum

M^+ m/e 355† (1%); m/e 353 (2%); m/e 340 (1%):
m/e 312† (6%); m/e 220† (100%); m/e 203† (16%);
m/e 135 (24%).

m* ~~135 (24%)~~ 187.3 † precision mass measured

measured mass	formula	calculated mass
355.1766	$C_{21}H_{25}NO_4$	355.1783
312.1599	$C_{19}H_{22}NO_3$	312.1600
220.1335	$C_{13}H_{18}NO_2$	220.1337
203.1072	$C_{13}H_{15}O_2$	203.1072

Sulphonic acid (LXXVI)

3-(4-methoxybenzoyl)-3-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine

(LXXV)

Prepared from XXXVII by cold cyclisation.

On basification an immediate precipitate was noticed which re-dissolved. When the mixture became basic no precipitate was present nor could any precipitate be reproduced by careful acidification. Extraction with chloroform gave no residue after drying (Mg SO_4) and removal of the solvent.

The aqueous solution was made slightly acid (pH 6.5) with hydrochloric acid, and allowed to stand for several days. White crystals (2g, m.p. 220° d) appeared which were filtered off and re-crystallised (prisms) from distilled water.

	C	H	N	S	(O)
Found	57.57	5.85	3.49	8.79%	(26.30%)
$C_{18}H_{21}NO_5S.\ H_2O$ requires	56.69	6.04	3.68	8.40%	(24.91%)

i.r. (spectrum page 154)	S - O stretching	690 cm^{-1}
	para disubstituted benzene ring	850 cm^{-1}
	SO_2 symmetric stretching	1010 cm^{-1}
	SO_2 asymmetric stretching	1170 cm^{-1}
	$>C = O$	1665 cm^{-1}
	- OH	3400 cm^{-1}

n.m.r. (spectrum page 155)

δ	int.	mult.	assignment.
2.0	3	s	CH_3 -
2.30 - 3.00	4	m	$-CH_2-CH_2-$ (ABCD pattern)
3.94	3	s	methoxyl
6.25	solvent residual		
7.0 - 7.2	4	t	Two overlapping doublets of AA'XX' pattern
7.70 - 7.80	2	d	Part of AA'XX'
8.0 - 8.1	2	d	Part of AA'XX'

This experiment was repeated. After basification (NaOH) the reaction mixture was extracted with diethyl ether (3 x 50 ml). The combined ether extract was washed once with water (25 ml), dried ($Mg SO_4$) and the ether removed under reduced pressure, giving a viscous pale yellow semi solid (500 mg) which would not crystallise.

	C	H	N
Found	77.26	7.23	4.48%
$C_{19}H_{21}NO_2$ requires	77.29	7.12	4.75%

i.r.	$>CO$	1665 cm^{-1}
	$>NH$	3400 cm^{-1}

n.m.r.

δ	int.	mult.	assignment.
1.10)	4	part of doublet	CH_3 + 1H
1.20 - 1.30)		with "shoulder"	of - CH_2-CH_2-
1.50	1*	s	$>$NH
2.3 - 3.3	3	m	3 x H of -CH_2-CH_2-
3.48	2	s	Ar-CH_2-N
3.60	3	s	methoxyl
6.62 - 6.76	2	d(J=9Hz))	asymmetrical para disubstituted
8.23 - 8.37	2	d(J=9Hz))	benzene ring.
6.70 - 7.0	4	m	aromatic protons of heterocycle.

* disappeared on deuteration.

Mass spectrum

M^+ m/e 295 (< 1%); m/e 280 (< 1%); m/e 160 (100%); m/e 135 (20%).

6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride

To 2-(3,4-dimethoxyphenyl)-ethylamine (36.2g, 0.2 mol) was added formaldehyde (6.6g as 40% aqueous solution i.e. 16.5 ml, 0.22 mol). Heat was evolved and the mixture was heated on a steam bath for 30 minutes. An excess of concentrated hydrochloric acid was added and the mixture slowly evaporated to dryness. Re-crystallisation of the solid from aqueous alcohol gave 30.0g (65.4%) of the base hydrochloride m.p. 251° (lit.[133] quotes 253°).

Unambiguous synthesis of 2-(4-methoxybenzoylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

α -Bromo-4-methoxyacetophenone (5.95g, 0.026 mol) dissolved in absolute alcohol (50 ml) was added dropwise to a refluxing mixture of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5g, ~~0.0q6~~ 0.026 mol) and anhydrous sodium carbonate in absolute alcohol (50 ml). After eight hours the mixture was cooled giving pale yellow crystals. Filtration and re-crystallisation from absolute alcohol gave 4g (45%) of product as pale yellow needles.

m.p. 121°

Mixed melting point with LXVIII m.p. 121°.

The i.r. spectrum was superimposable on that obtained from LXVIII.

Cyclisation of 2-(4-methoxybenzylamino)-2-spirocyclohexyl-acetonitrile (1) in the presence of a nucleophile.

1g (1) was mixed with veratrole (1 ml) and added to concentrated sulphuric acid (20 ml) at $0^{o}C$. After eighteen hours at room temperature the mixture was poured on to crushed ice and basified with 5N sodium hydroxide. The resulting precipitate was filtered off, dried and re-crystallised from petroleum ether (b.p. 60-80^{o}).

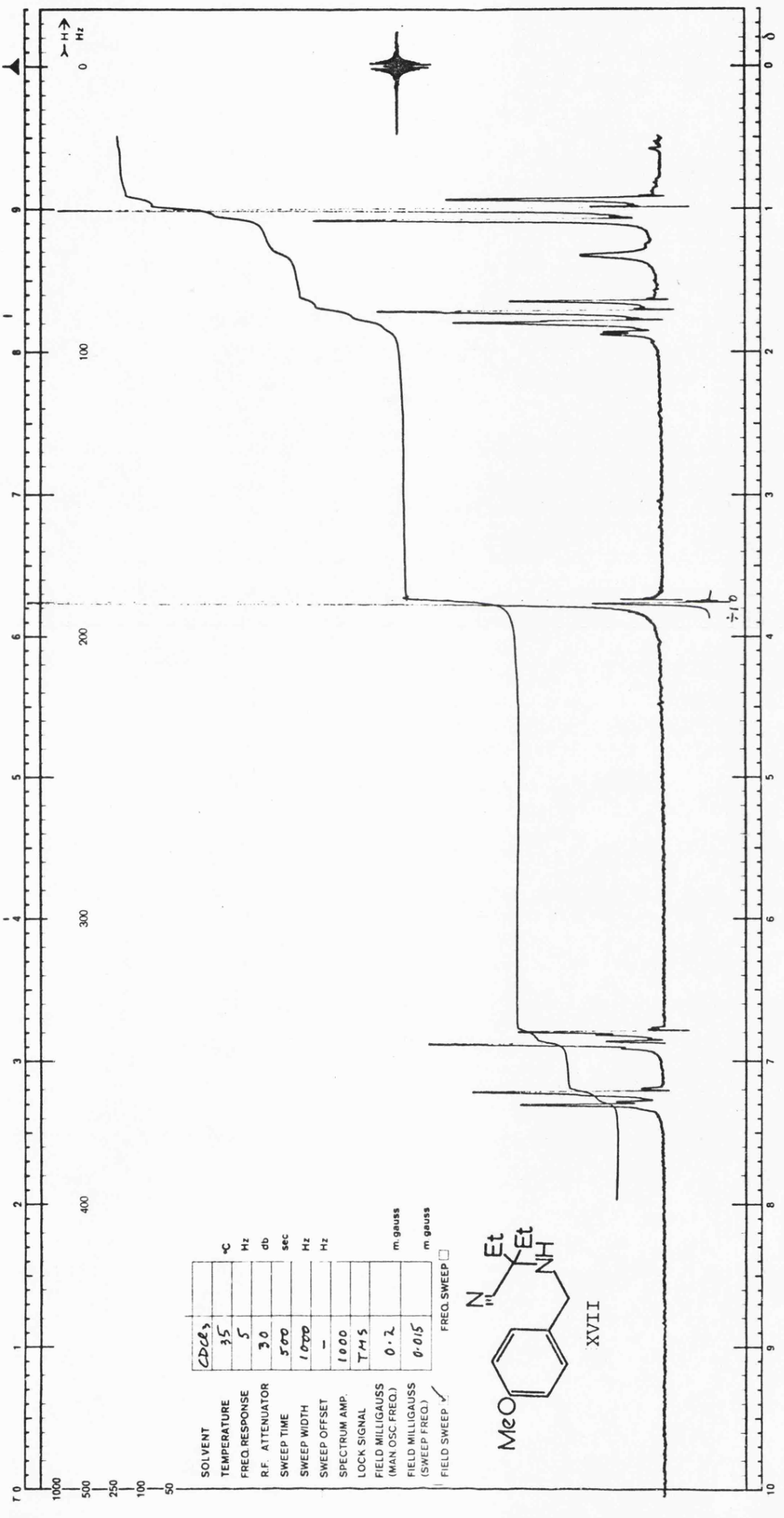
Yield 800 mg m.p. 92^{o}.

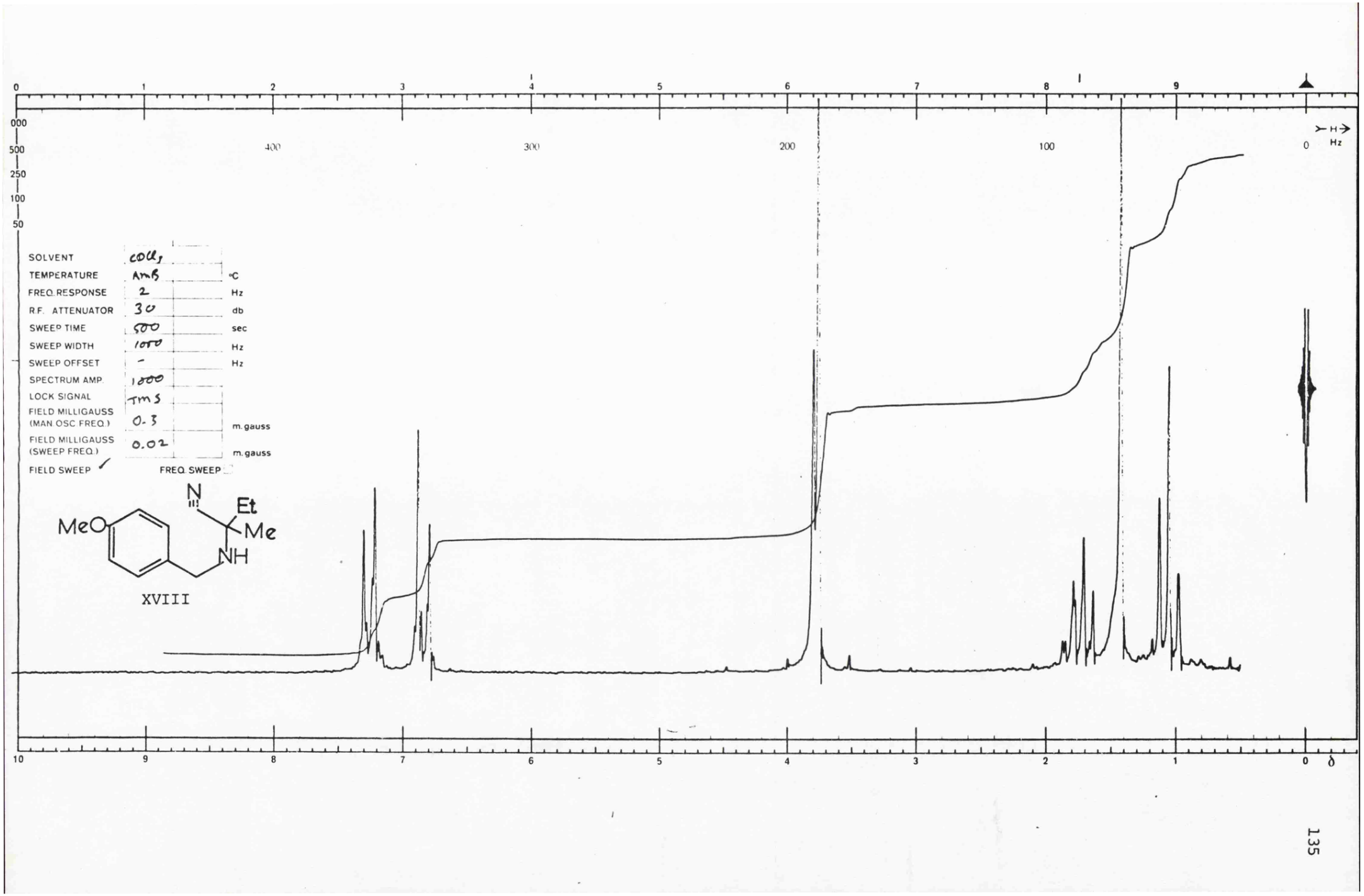
Mixed melting point with 4-(4-methoxyphenyl)-5-spiro cyclohexyl-3-imidazoline[49] 92^{o}.

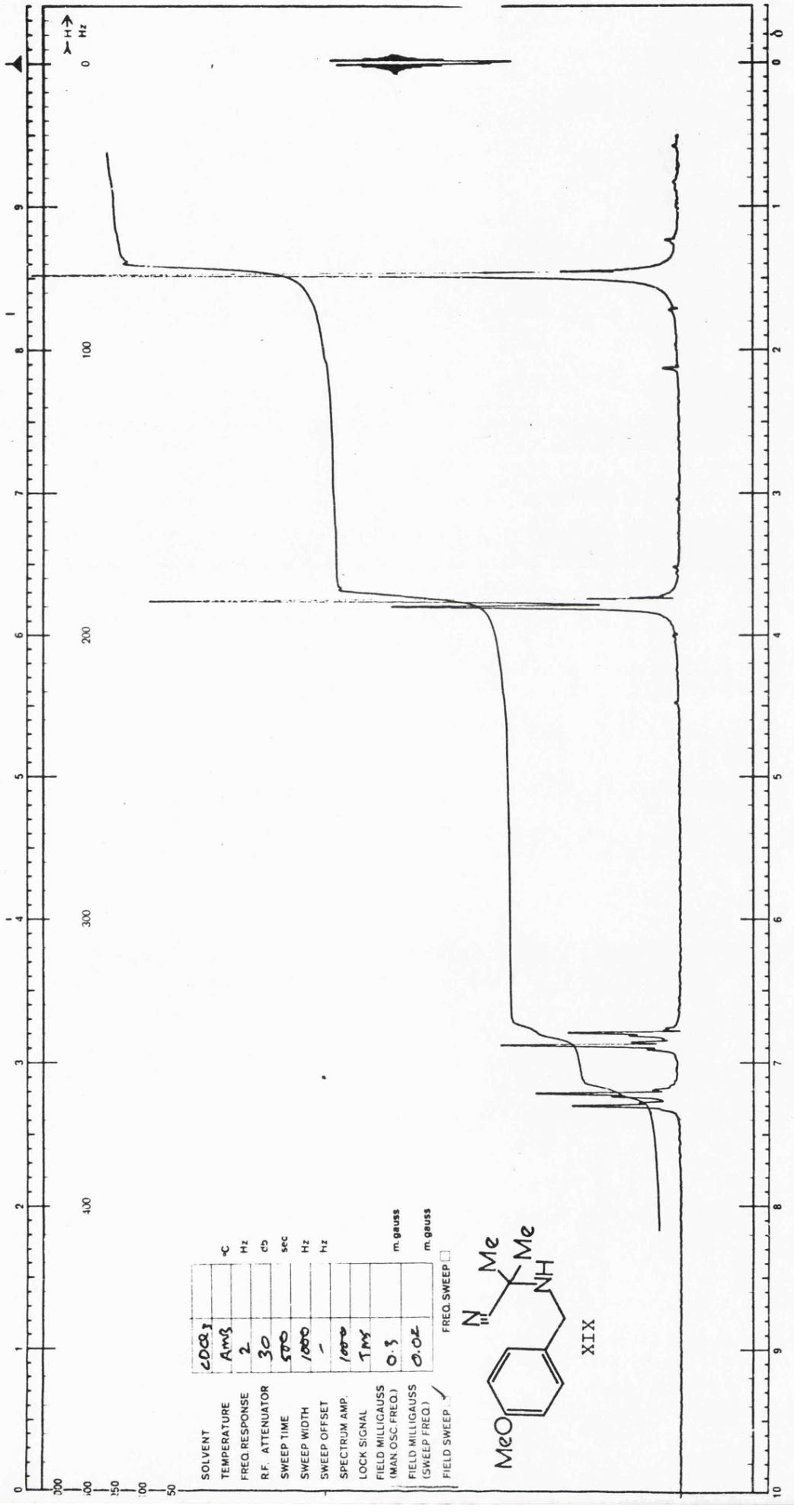
The above experiment was repeated using

1) anisole (1 ml)

2) benzene (1 ml) in place of veratrole but with identical results.

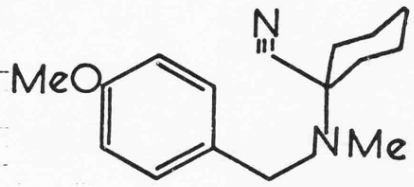

SOLVENT
TEMPERATURE
FREQ. RESPONSE
R.F. ATTENUATOR
SWEEP TIME
SWEEP WIDTH
SWEEP OFFSET
SPECTRUM AMP.
LOCK SIGNAL
FIELD MILLIGAUSS (MAN OSC FREQ.)
FIELD MILLIGAUSS (SWEEP FREQ.)
FIELD SWEEP ✓
FREQ. SWEEP
CDCl3
35
5
30
500
1000
–
1000
TMS
0·2
0·015
°C
Hz
db
sec
Hz
Hz
m. gauss
m. gauss
MeO
Et
Et
NH
N
XVII


SOLVENT CCl4
TEMPERATURE Amb °C
FREQ. RESPONSE 2 Hz
R.F. ATTENUATOR 30 db
SWEEP TIME 500 sec
SWEEP WIDTH 1000 Hz
SWEEP OFFSET - Hz
SPECTRUM AMP. 1000
LOCK SIGNAL TMS
FIELD MILLIGAUSS (MAN OSC FREQ.) 0.3 m.gauss
FIELD MILLIGAUSS (SWEEP FREQ.) 0.02 m.gauss
FIELD SWEEP ✓ FREQ. SWEEP
MeO
N
Et
Me
NH
XVIII
0 1 2 3 4 5 6 7 8 9
000 500 250 100 50
400 300 200 100 0 Hz
10 9 8 7 6 5 4 3 2 1 0 δ


SOLVENT
TEMPERATURE
FREQ. RESPONSE
R.F. ATTENUATOR
SWEEP TIME
SWEEP WIDTH
SWEEP OFFSET
SPECTRUM AMP.
LOCK SIGNAL
FIELD MILLIGAUSS (MAN. OSC. FREQ.)
FIELD MILLIGAUSS (SWEEP FREQ.)
FIELD SWEEP
FREQ. SWEEP
CDCl3
AMB
2
30
500
1000
-
1000
TMS
0.3
0.02
°C
Hz
db
sec
Hz
Hz
m. gauss
m. gauss
MeO
Me
Me
NH
N
XIX

SPECTRUM NO.
DATE
FREQ.
NUCLEUS H
SAMPLE XT A55

SOLVENT	$CDCl_3$
CONC.	25 mg
REFERENCE	TMS
LOCK	EXT
TEMP.	28 °C
R. F. LEVEL	40
A. F. LEVEL ANALYTICAL	4-5
LOCK	
SD	
AMPLITUDE ANALYTICAL	x 10-5
LOCK	
INTEGRATOR	
FILTER	20
OFFSET	Hz / PPM
FREQ. FIELD / FREQ. (FIELD)	



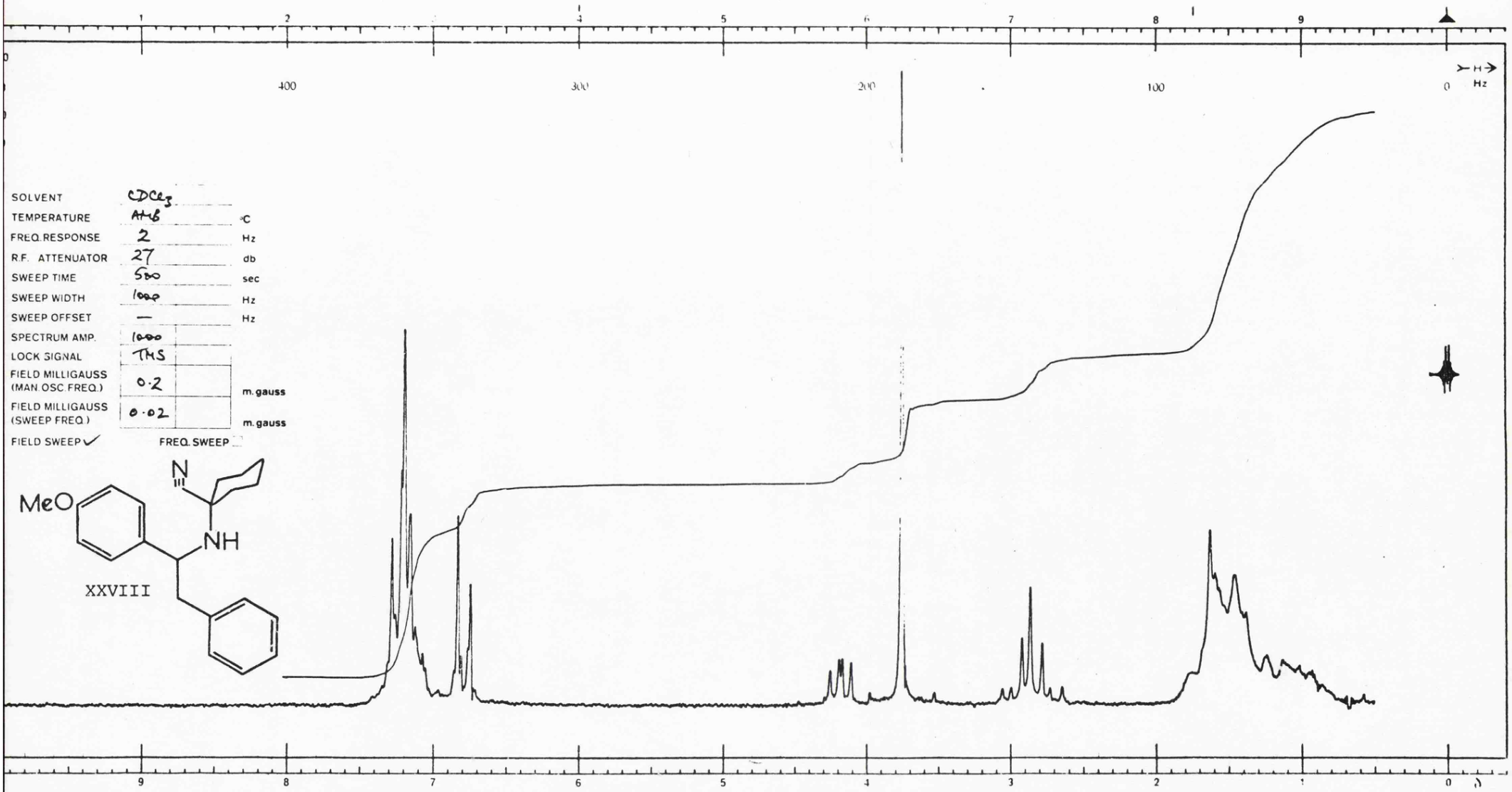
XXII

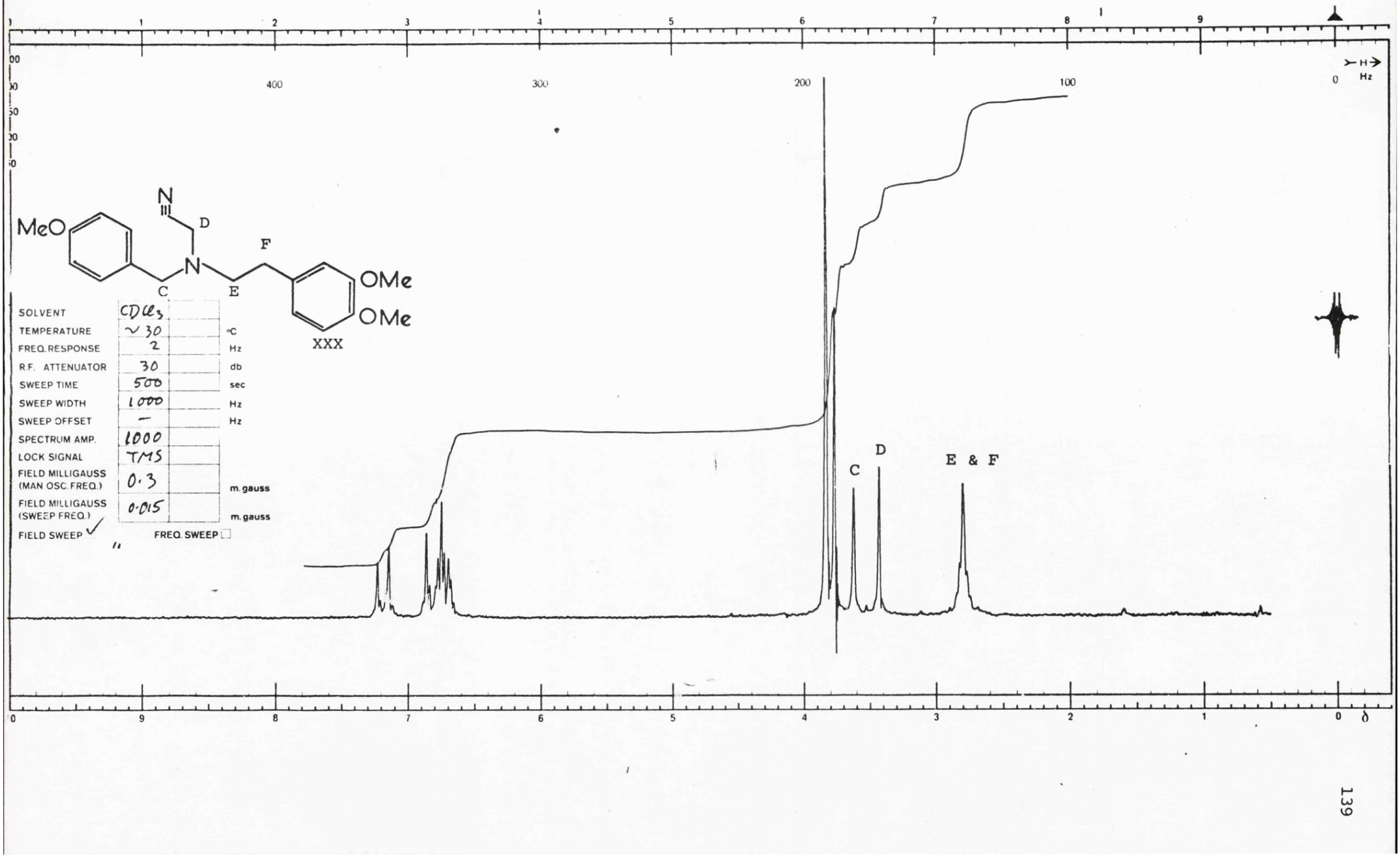
OPERATOR
REMARKS:

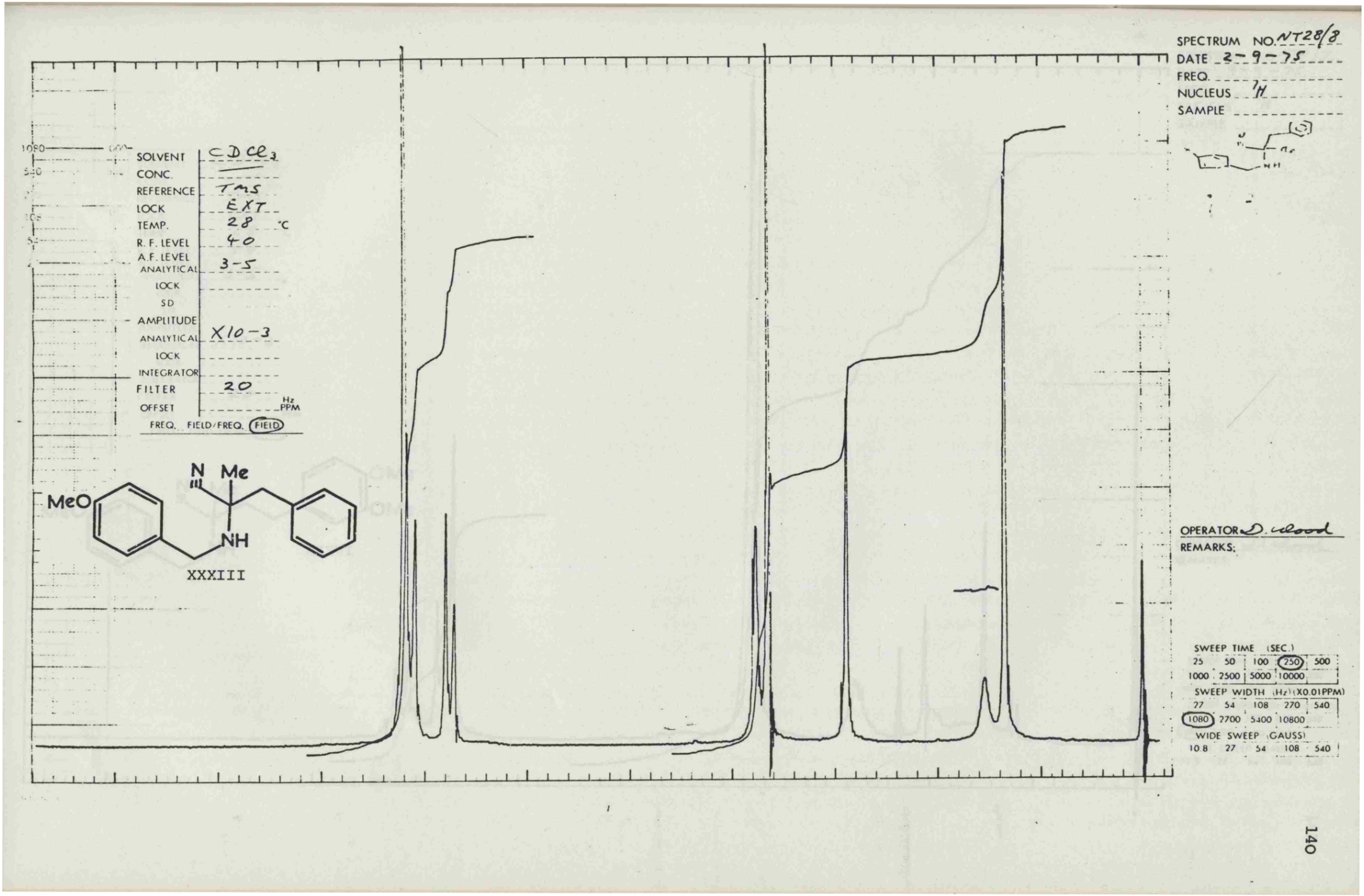
SWEEP TIME (SEC.)
25 50 (100) (250) 500
1000 2500 5000 10000

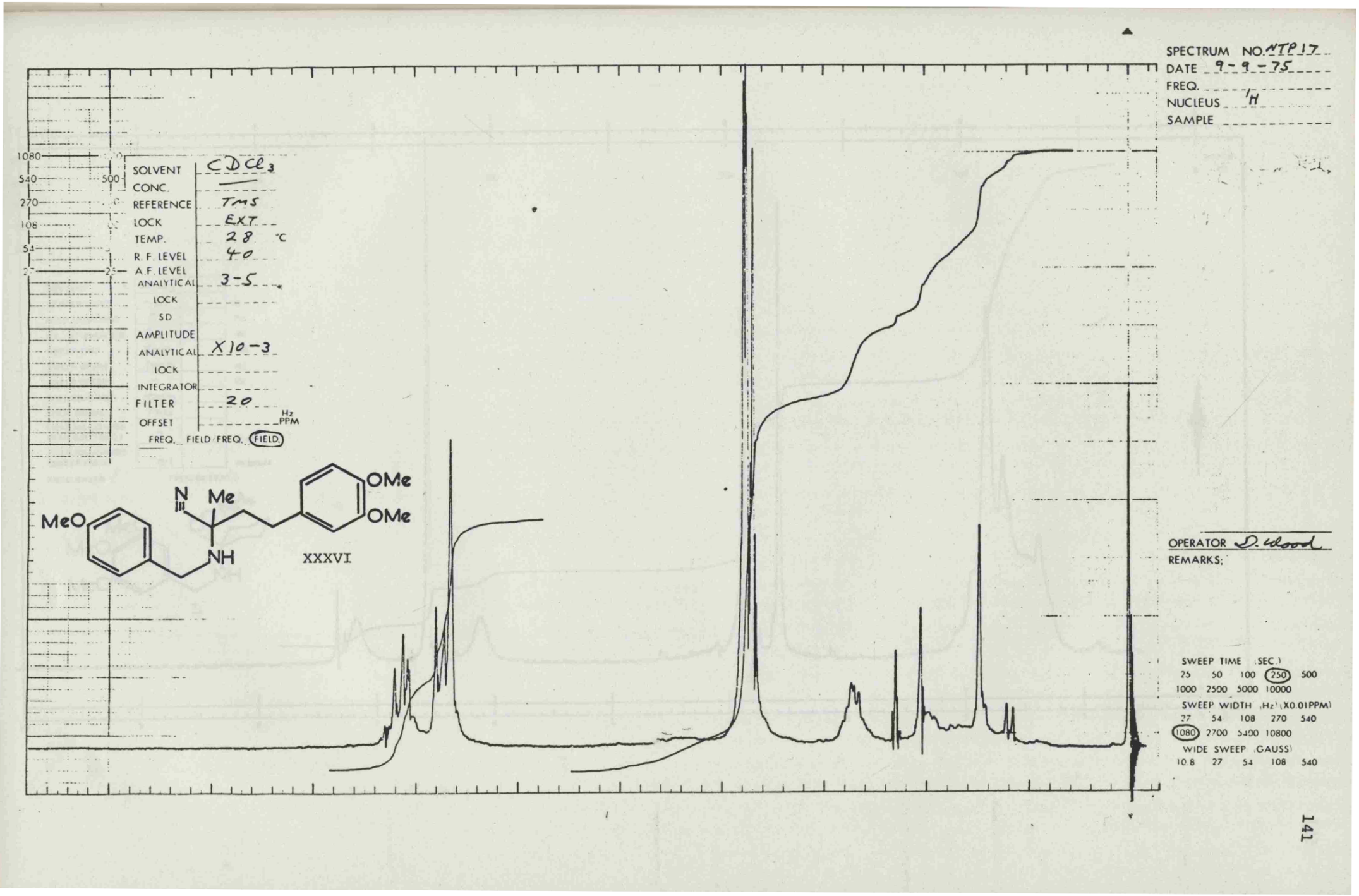
SWEEP WIDTH (Hz) (X0.01PP
27 54 108 270 540
(1080) 2700 5400 10800

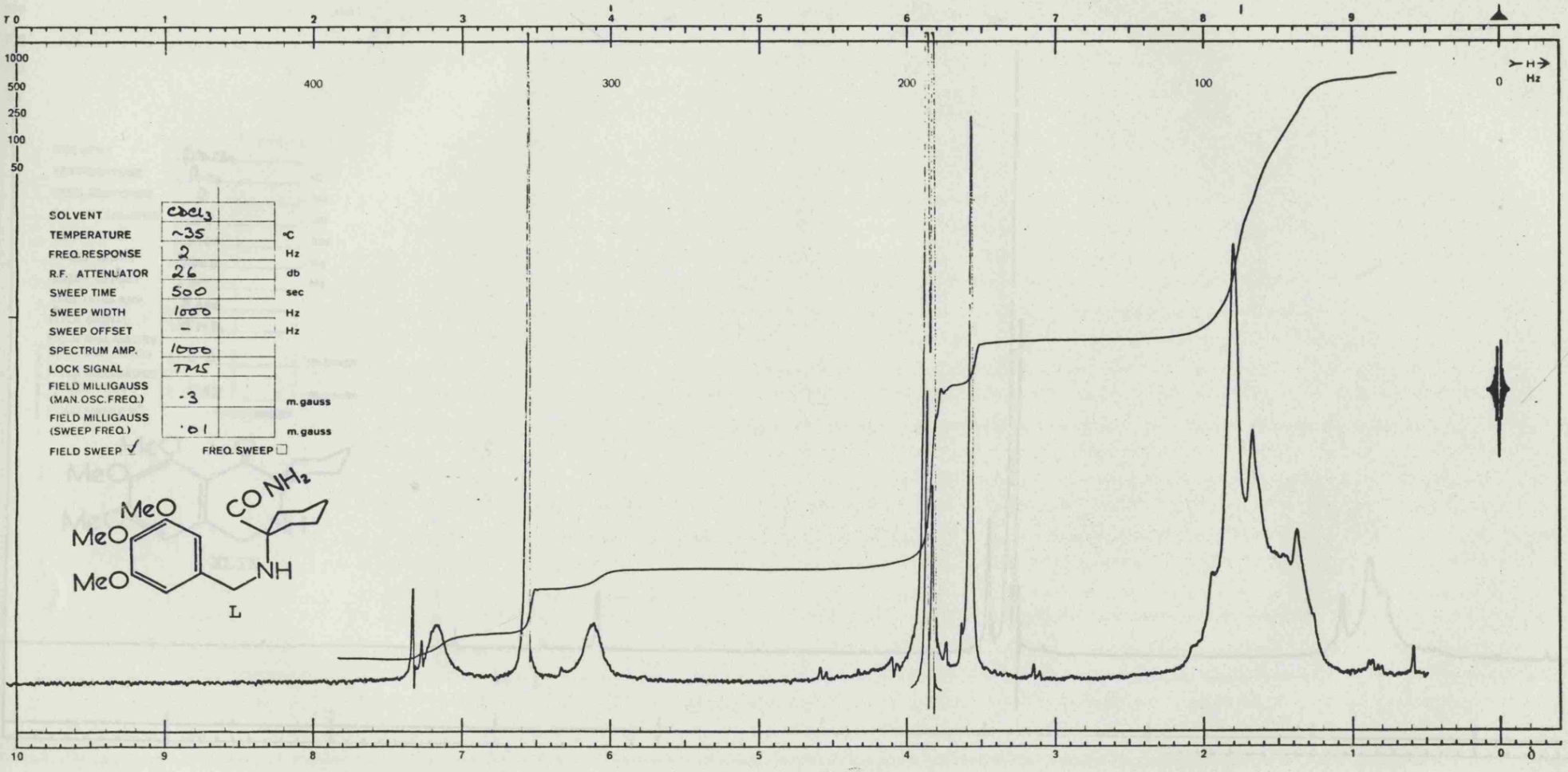
WIDE SWEEP (GAUSS)
10.8 27 54 108 540

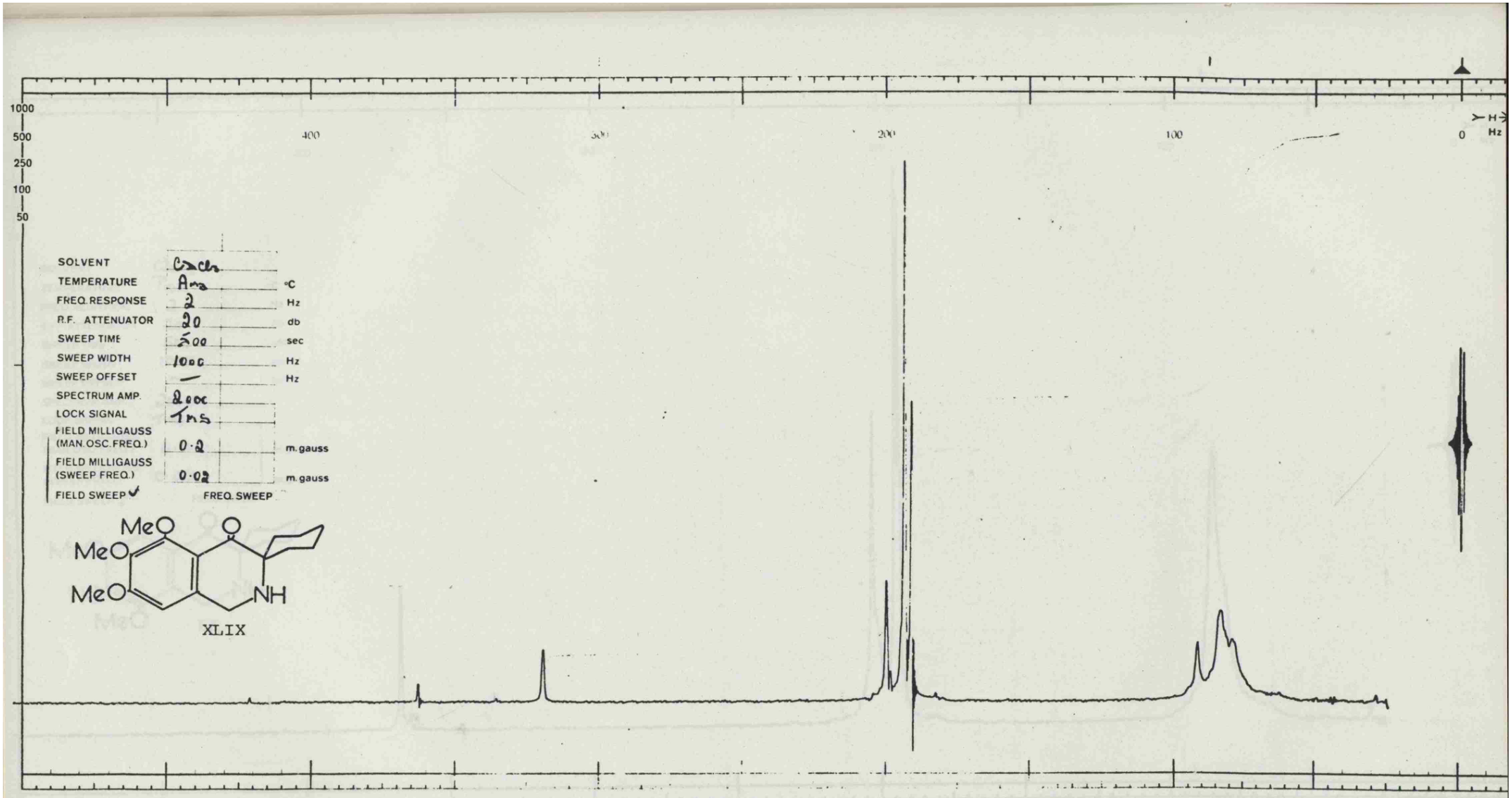

400
300
200
100
0
Hz
SOLVENT CDCl3
TEMPERATURE AMB °C
FREQ. RESPONSE 2 Hz
R.F. ATTENUATOR 27 db
SWEEP TIME 500 sec
SWEEP WIDTH 1000 Hz
SWEEP OFFSET — Hz
SPECTRUM AMP. 1000
LOCK SIGNAL TMS
FIELD MILLIGAUSS (MAN OSC FREQ.) 0.2 m. gauss
FIELD MILLIGAUSS (SWEEP FREQ.) 0.02 m. gauss
FIELD SWEEP ✓ FREQ. SWEEP
MeO
N
NH
XXVIII
9
8
7
6
5
4
3
2
1
0


MeO
N
D
F
N
C
E
OMe
OMe
XXX
SOLVENT CDCl3
TEMPERATURE ~30 °C
FREQ. RESPONSE 2 Hz
R.F. ATTENUATOR 30 db
SWEEP TIME 500 sec
SWEEP WIDTH 1000 Hz
SWEEP OFFSET — Hz
SPECTRUM AMP. 1000
LOCK SIGNAL TMS
FIELD MILLIGAUSS (MAN OSC. FREQ.) 0.3 m. gauss
FIELD MILLIGAUSS (SWEEP FREQ.) 0.015 m. gauss
FIELD SWEEP ✓
FREQ. SWEEP □
C
D
E & F
400
300
200
100
0 Hz
δ

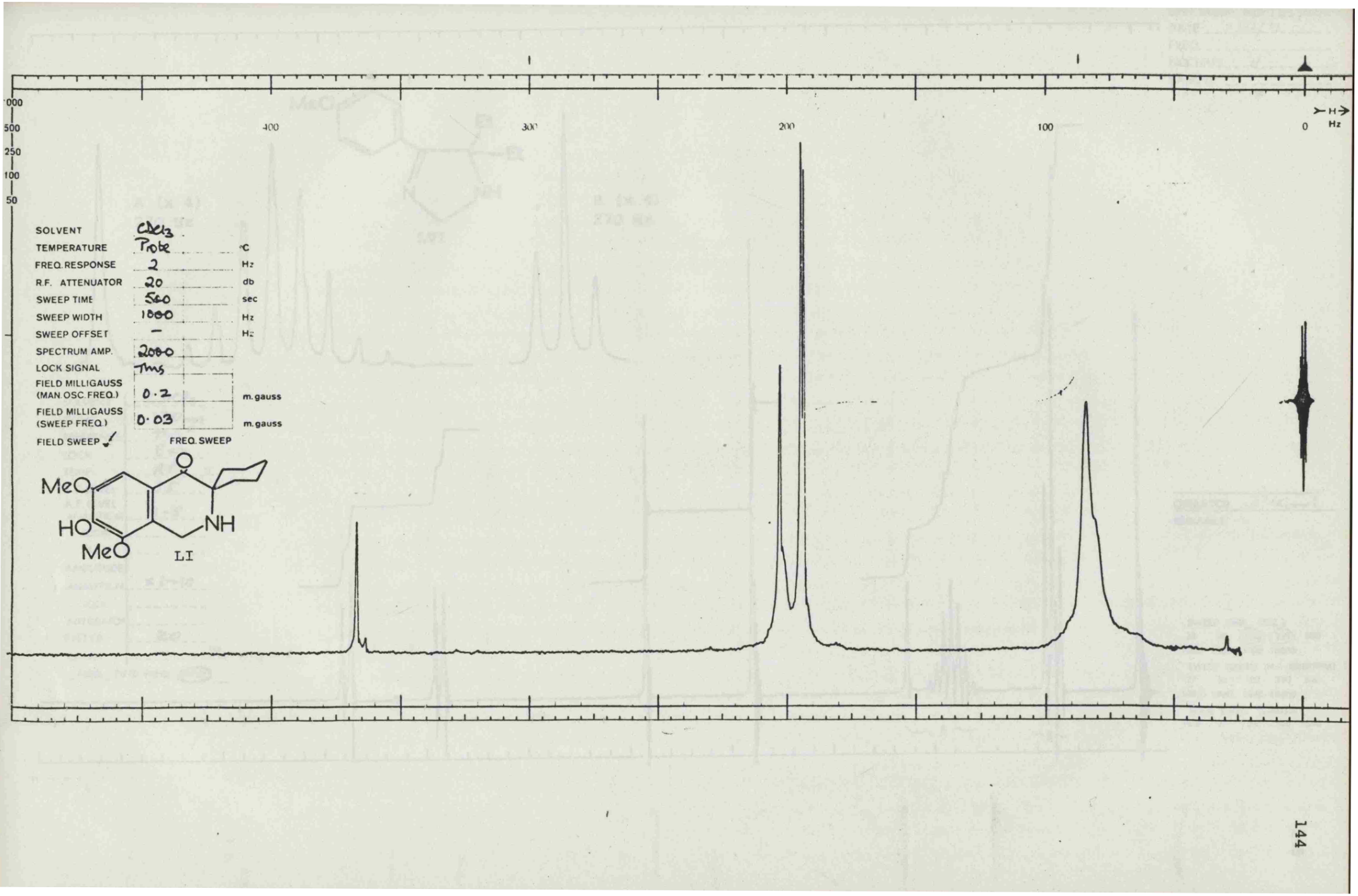

SPECTRUM NO. NT28/8
DATE 3-9-75
FREQ.
NUCLEUS 1H
SAMPLE
SOLVENT CDCl3
CONC.
REFERENCE TMS
LOCK EXT
TEMP. 28 °C
R. F. LEVEL 40
A. F. LEVEL ANALYTICAL 3-5
LOCK
SD
AMPLITUDE ANALYTICAL X10-3
LOCK
INTEGRATOR
FILTER 20
OFFSET Hz PPM
FREQ. FIELD/FREQ. (FIELD)
MeO
N
Me
NH
XXXIII
OPERATOR D. Wood
REMARKS:
SWEEP TIME (SEC.)
25 50 100 (250) 500
1000 2500 5000 10000
SWEEP WIDTH (Hz) (X0.01PPM)
27 54 108 270 540
(1080) 2700 5400 10800
WIDE SWEEP (GAUSS)
10.8 27 54 108 540

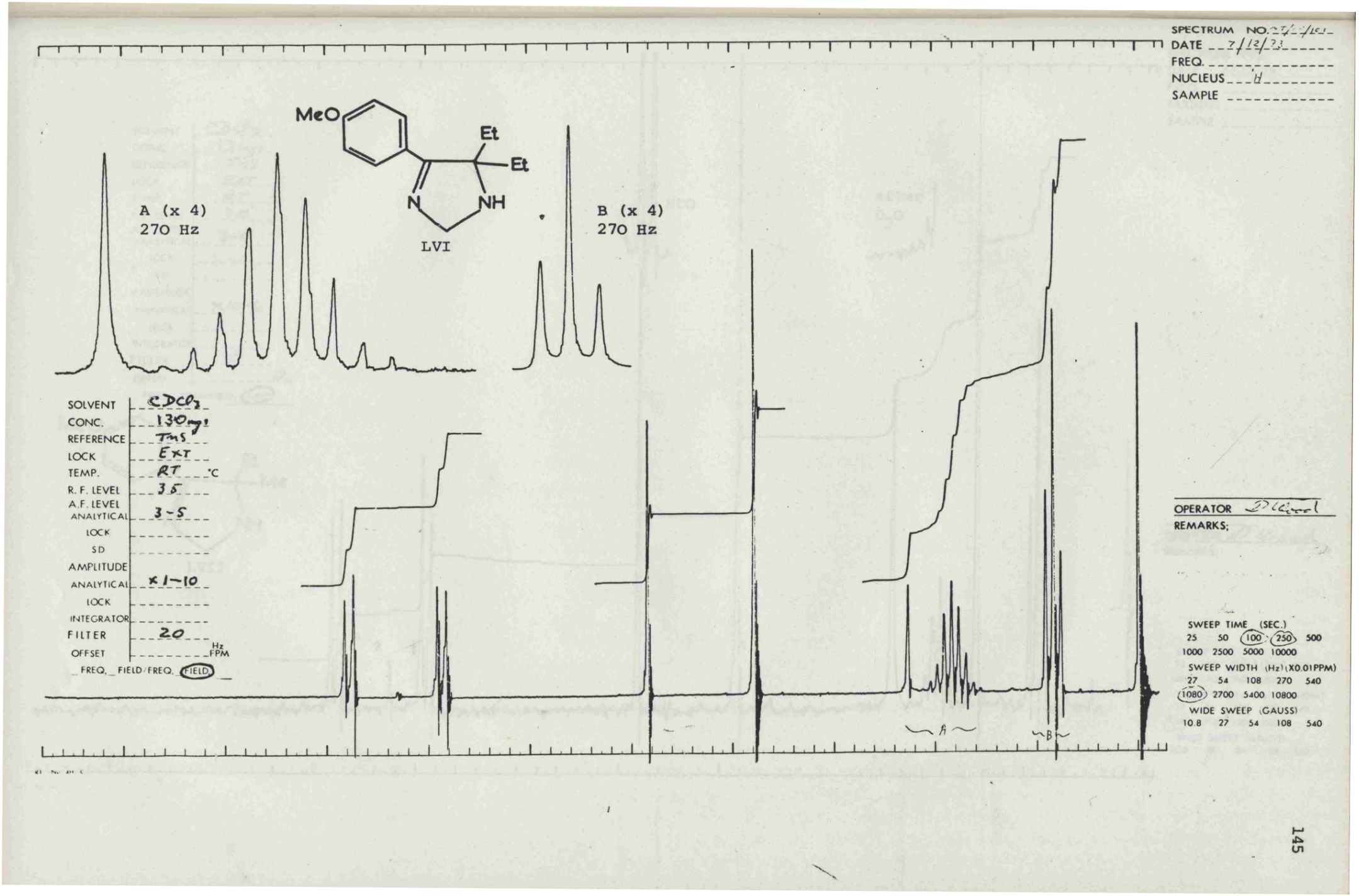

SPECTRUM NO. NTP17
DATE 9-9-75
FREQ.
NUCLEUS 1H
SAMPLE
SOLVENT CDCl3
CONC.
REFERENCE TMS
LOCK EXT
TEMP. 28 °C
R. F. LEVEL 40
A. F. LEVEL
ANALYTICAL 3-5
LOCK
SD
AMPLITUDE
ANALYTICAL X10-3
LOCK
INTEGRATOR
FILTER 20
OFFSET Hz PPM
FREQ. FIELD FREQ. (FIELD)
1080
540
270
108
54
27
500
25
MeO
N
Me
NH
OMe
OMe
XXXVI
OPERATOR D. Wood
REMARKS:
SWEEP TIME (SEC.)
25 50 100 (250) 500
1000 2500 5000 10000
SWEEP WIDTH (Hz) (X0.01PPM)
27 54 108 270 540
(1080) 2700 5400 10800
WIDE SWEEP (GAUSS)
10.8 27 54 108 540


SOLVENT CDCl3
TEMPERATURE ~35 °C
FREQ. RESPONSE 2 Hz
R.F. ATTENUATOR 26 db
SWEEP TIME 500 sec
SWEEP WIDTH 1000 Hz
SWEEP OFFSET - Hz
SPECTRUM AMP. 1000
LOCK SIGNAL TMS
FIELD MILLIGAUSS (MAN. OSC. FREQ.) -3 m.gauss
FIELD MILLIGAUSS (SWEEP FREQ.) ·01 m.gauss
FIELD SWEEP ✓ FREQ. SWEEP □
MeO
MeO
MeO
CONH2
NH
L
1000
500
250
100
50
400
300
200
100
0 Hz
0
1
2
3
4
5
6
7
8
9
10


1000
500
250
100
50
400
300
200
100
0
Hz
SOLVENT
CDCl3
TEMPERATURE
Amb
°C
FREQ. RESPONSE
2
Hz
R.F. ATTENUATOR
20
db
SWEEP TIME
500
sec
SWEEP WIDTH
1000
Hz
SWEEP OFFSET
—
Hz
SPECTRUM AMP.
2 00
LOCK SIGNAL
Ins
FIELD MILLIGAUSS (MAN. OSC. FREQ.)
0·2
m. gauss
FIELD MILLIGAUSS (SWEEP FREQ.)
0·02
m. gauss
FIELD SWEEP
FREQ. SWEEP
MeO
MeO
MeO
NH
O
O

XLIX

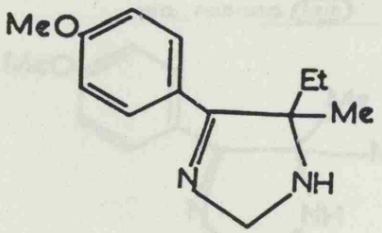

500
400
300
200
100
0
Hz
1000
500
250
100
50
SOLVENT CDCl3
TEMPERATURE Probe °C
FREQ. RESPONSE 2 Hz
R.F. ATTENUATOR 20 db
SWEEP TIME 560 sec
SWEEP WIDTH 1000 Hz
SWEEP OFFSET — Hz
SPECTRUM AMP. 2000
LOCK SIGNAL TMS
FIELD MILLIGAUSS (MAN. OSC. FREQ.) 0·2 m.gauss
FIELD MILLIGAUSS (SWEEP FREQ.) 0·03 m.gauss
FIELD SWEEP
FREQ. SWEEP
MeO
HO
MeO
NH
LI
144


SPECTRUM NO. 27-1/101
DATE 7/12/73
FREQ.
NUCLEUS H
SAMPLE
MeO
Et
Et
N
NH
LVI
A (x 4)
270 Hz
B (x 4)
270 Hz
SOLVENT CDCl3
CONC. 130mg
REFERENCE TMS
LOCK EXT
TEMP. RT °C
R. F. LEVEL 35
A.F. LEVEL
ANALYTICAL 3-5
LOCK
SD
AMPLITUDE
ANALYTICAL x1-10
LOCK
INTEGRATOR
FILTER 20
OFFSET Hz FPM
FREQ. FIELD/FREQ. FIELD
OPERATOR
REMARKS;
SWEEP TIME (SEC.)
25 50 100 250 500
1000 2500 5000 10000
SWEEP WIDTH (Hz)(X0.01PPM)
27 54 108 270 540
1080 2700 5400 10800
WIDE SWEEP (GAUSS)
10.8 27 54 108 540
A
B

SPECTRUM NO. _____
DATE 25/1/74
FREQ. _____
NUCLEUS _____
SAMPLE _____

SOLVENT	$CDCl_3$
CONC.	13 mgs
REFERENCE	TMS
LOCK	EXT
TEMP.	RT °C
R. F. LEVEL	40
A. F. LEVEL ANALYTICAL	3-9
LOCK	
SD	
AMPLITUDE ANALYTICAL	X10-6
LOCK	
INTEGRATOR	
FILTER	10
OFFSET	Hz / PPM

FREQ. FIELD/FREQ. (FIELD)



LVII

HDO

after D_2O

OPERATOR: D Wood

REMARKS:

SWEEP TIME (SEC.)
25 50 (100) (250) 500
1000 2500 5000 10000

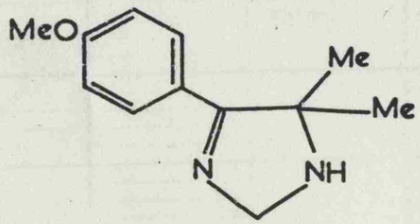
SWEEP WIDTH (Hz)(X0.01PPM)
27 54 108 270 540
(1080) 2700 5400 10800

WIDE SWEEP (GAUSS)
10.8 27 54 108 540

SPECTRUM NO. VT/15
DATE 17/1/76
FREQ.
NUCLEUS
SAMPLE

SOLVENT	$CDCl_3$
CONC.	11 mgs
REFERENCE	TMS
LOCK	EXT
TEMP.	RT °C
R. F. LEVEL	35
A.F. LEVEL ANALYTICAL	3-5
LOCK	
SD	
AMPLITUDE ANALYTICAL	X 10-5
LOCK	
INTEGRATOR	
FILTER	10
OFFSET Hz PPM	

FREQ. FIELD / FREQ. (FIELD)



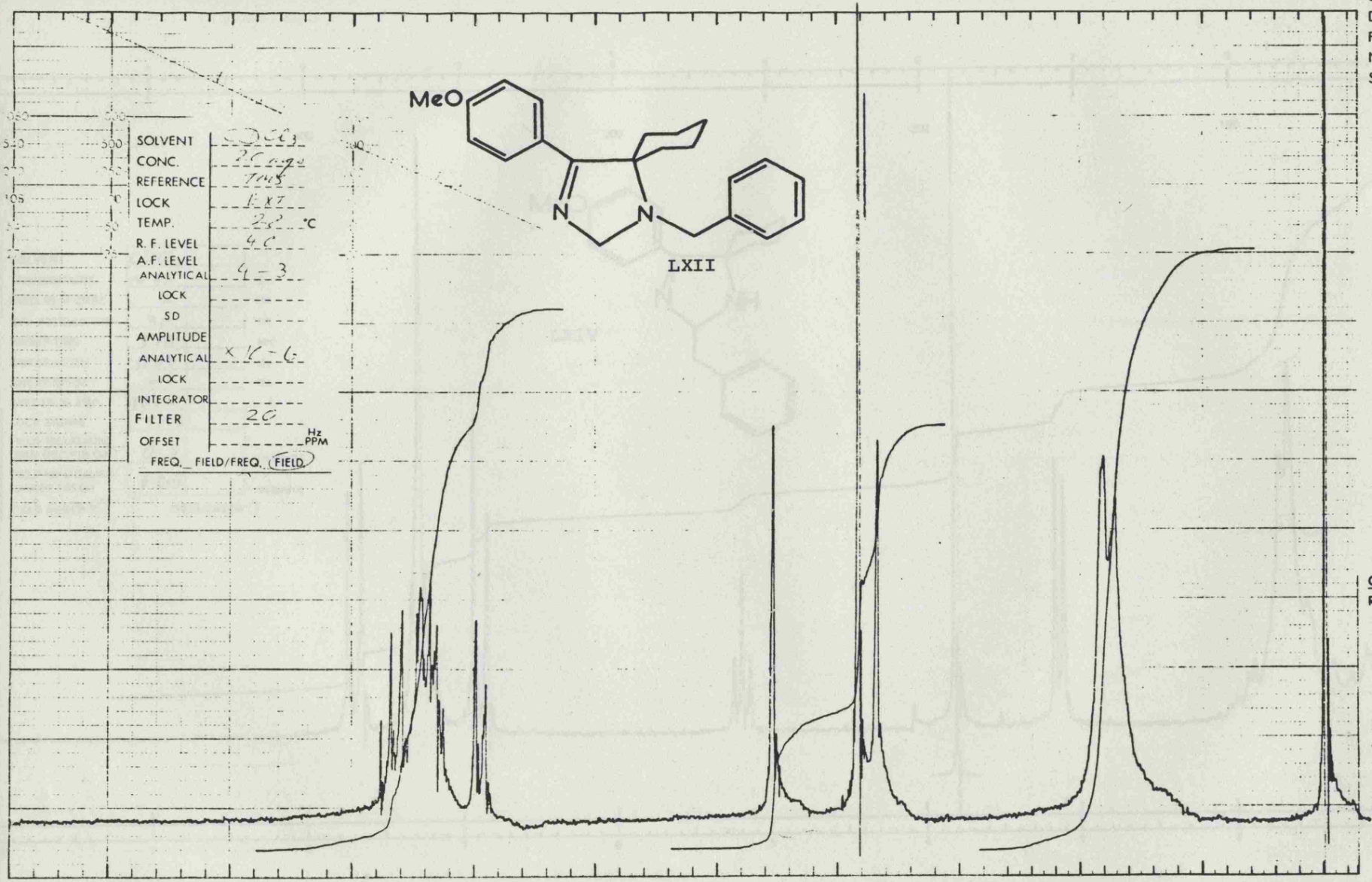
LVIII

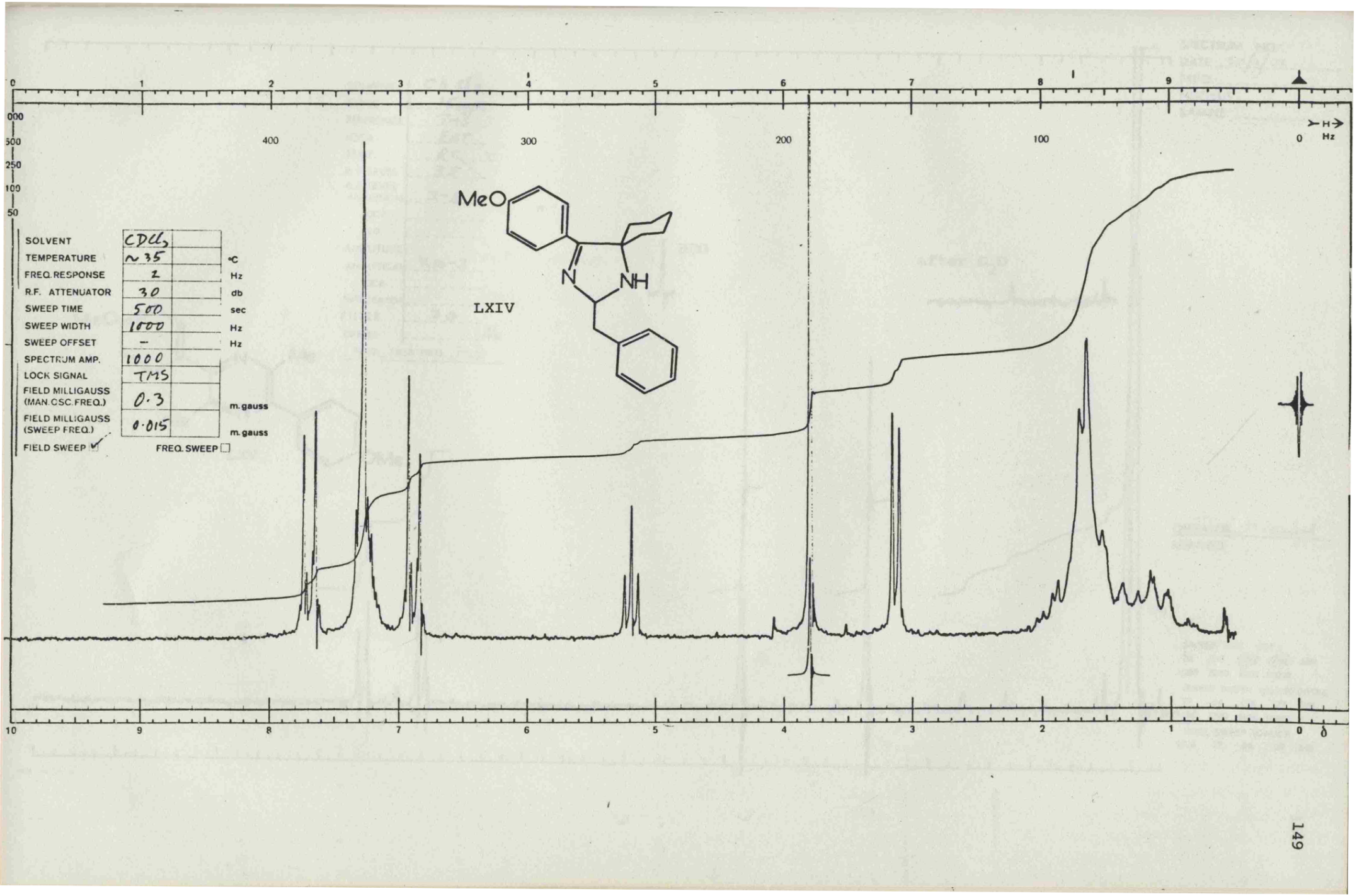
OPERATOR
REMARKS;

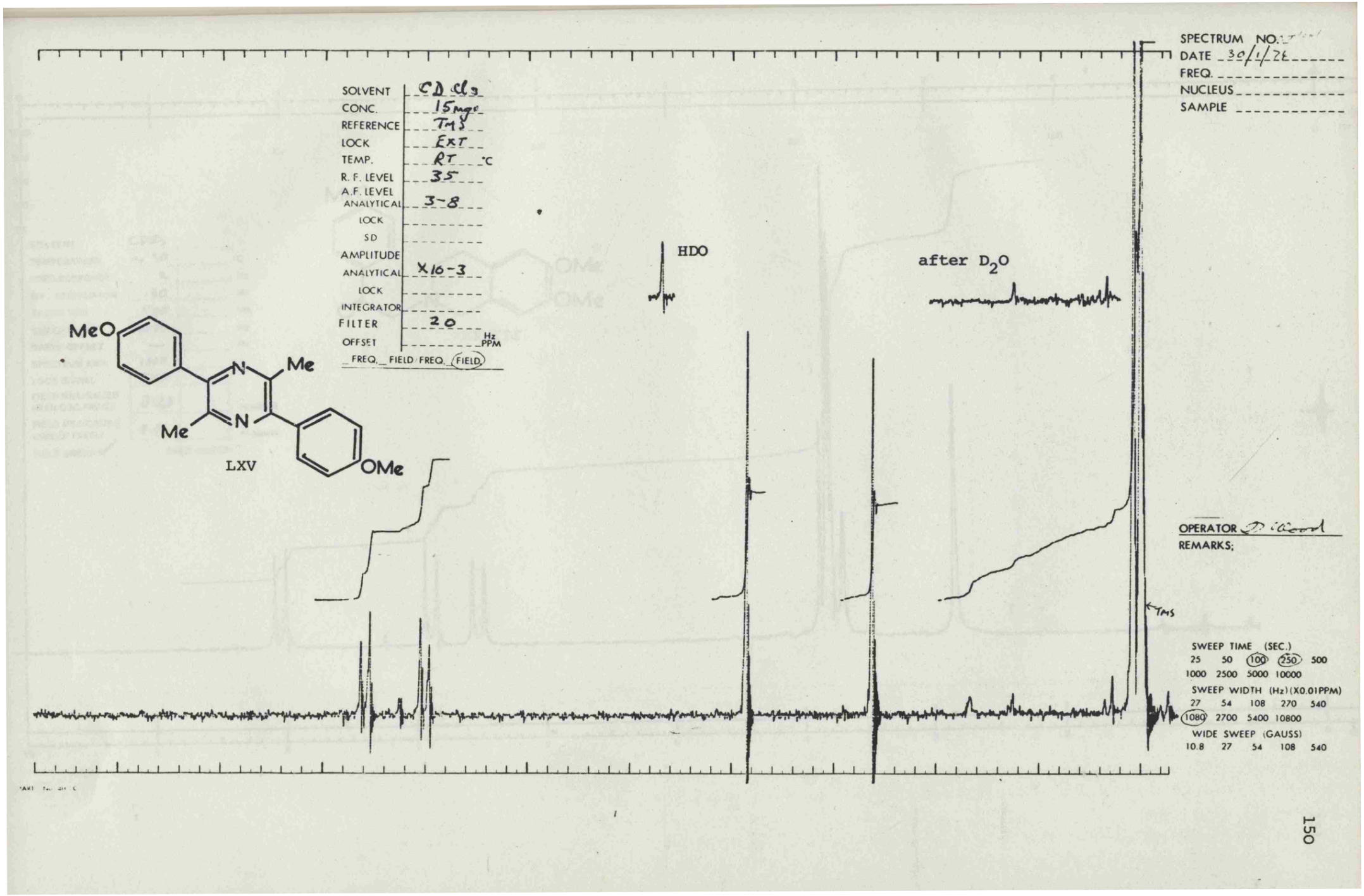
SWEEP TIME (SEC.)
25 50 (100) (250) 500
1000 2500 5000 10000

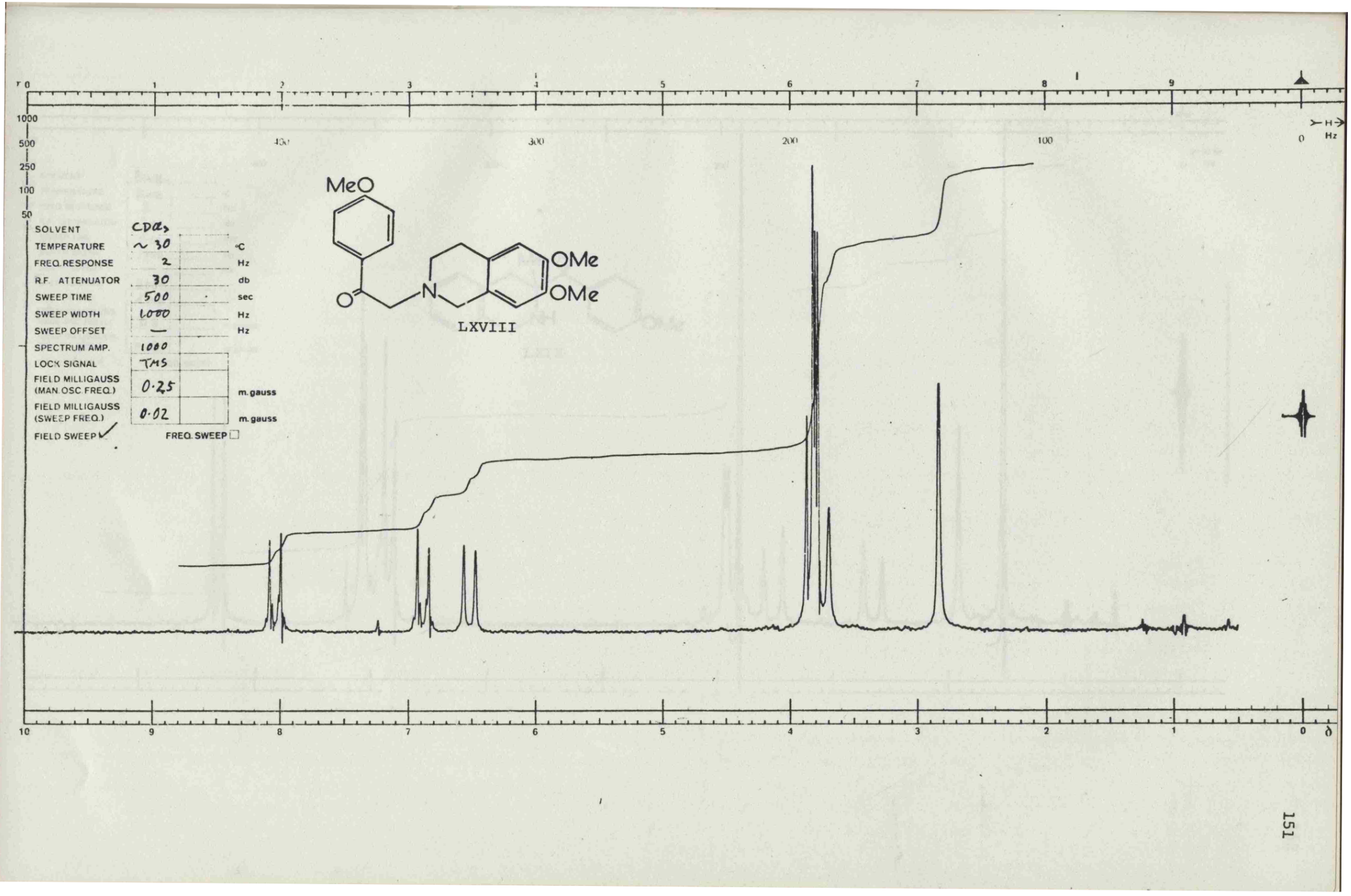
SWEEP WIDTH (Hz^1)(X0.01PPA^1)
27 54 108 270 540
(1080) 2700 5400 10800

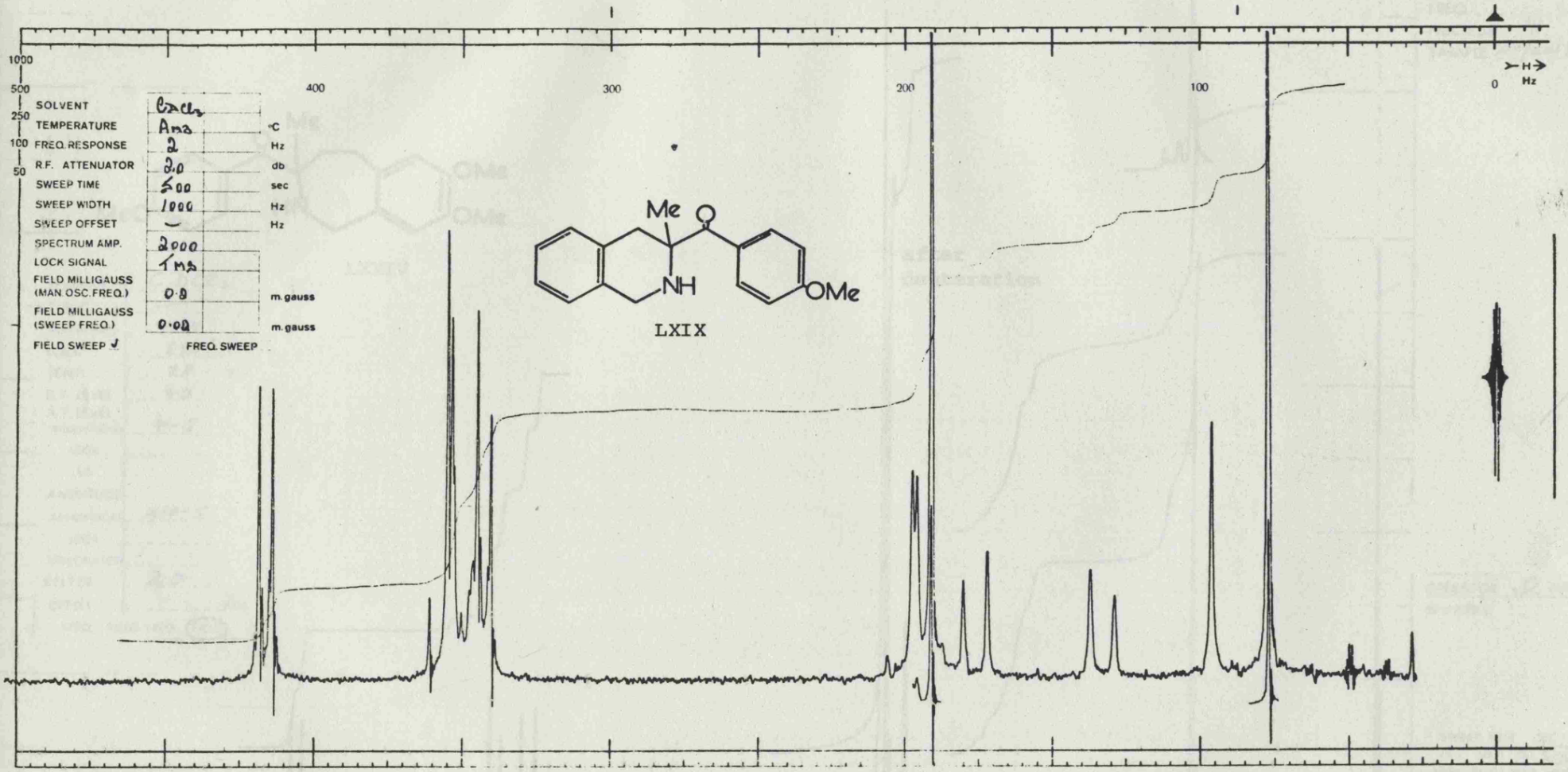
WIDE SWEEP (GAUSS)
10.8 27 54 108 540


MeO
N
N
LXII
SOLVENT CDCl3
CONC. 20 mg%
REFERENCE TMS
LOCK INT
TEMP. 33 °C
R. F. LEVEL 4C
A.F. LEVEL
ANALYTICAL 4-3
LOCK
SD
AMPLITUDE
ANALYTICAL X1-6
LOCK
INTEGRATOR
FILTER 20
OFFSET Hz PPM
FREQ. FIELD/FREQ. (FIELD)
SPECTRUM NO. LT/BM/5
DATE 9-1-75
FREQ.
NUCLEUS H
SAMPLE
OPERATOR
REMARKS:
SWEEP TIME (SEC.)
25 50 100 (250) 500
1000 2500 5000 10000
SWEEP WIDTH (Hz) (X0.01PPM)
27 54 108 270 540
(1080) 2700 5400 10800
WIDE SWEEP (GAUSS)
10.8 27 54 108 540

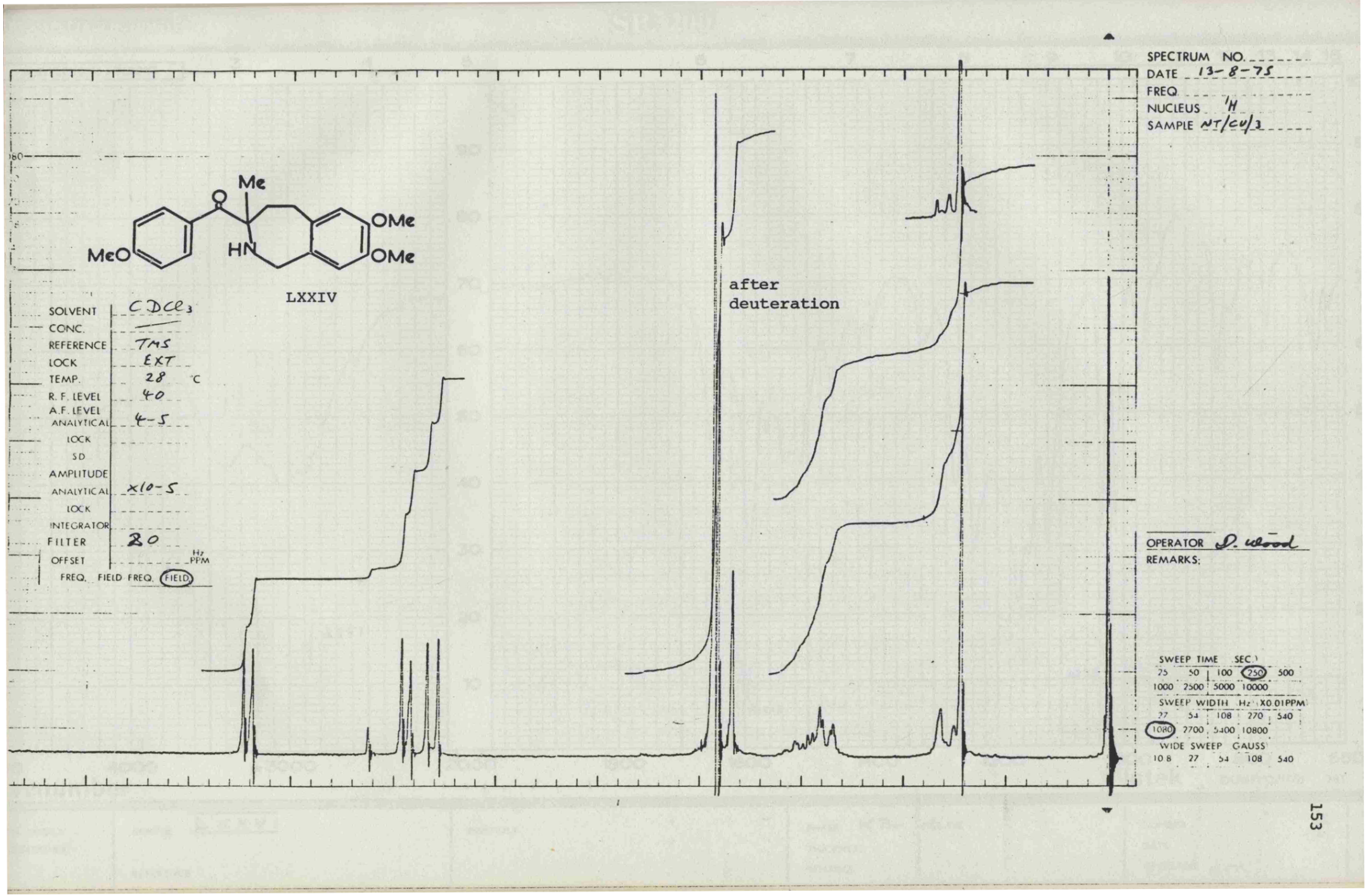

MeO
N
NH
LXIV
SOLVENT CDCl3
TEMPERATURE ~35 °C
FREQ. RESPONSE 2 Hz
R.F. ATTENUATOR 30 db
SWEEP TIME 500 sec
SWEEP WIDTH 1000 Hz
SWEEP OFFSET -- Hz
SPECTRUM AMP. 1000
LOCK SIGNAL TMS
FIELD MILLIGAUSS (MAN. OSC. FREQ.) 0.3 m.gauss
FIELD MILLIGAUSS (SWEEP FREQ.) 0.015 m.gauss
FIELD SWEEP ✓
FREQ. SWEEP
δ
Hz

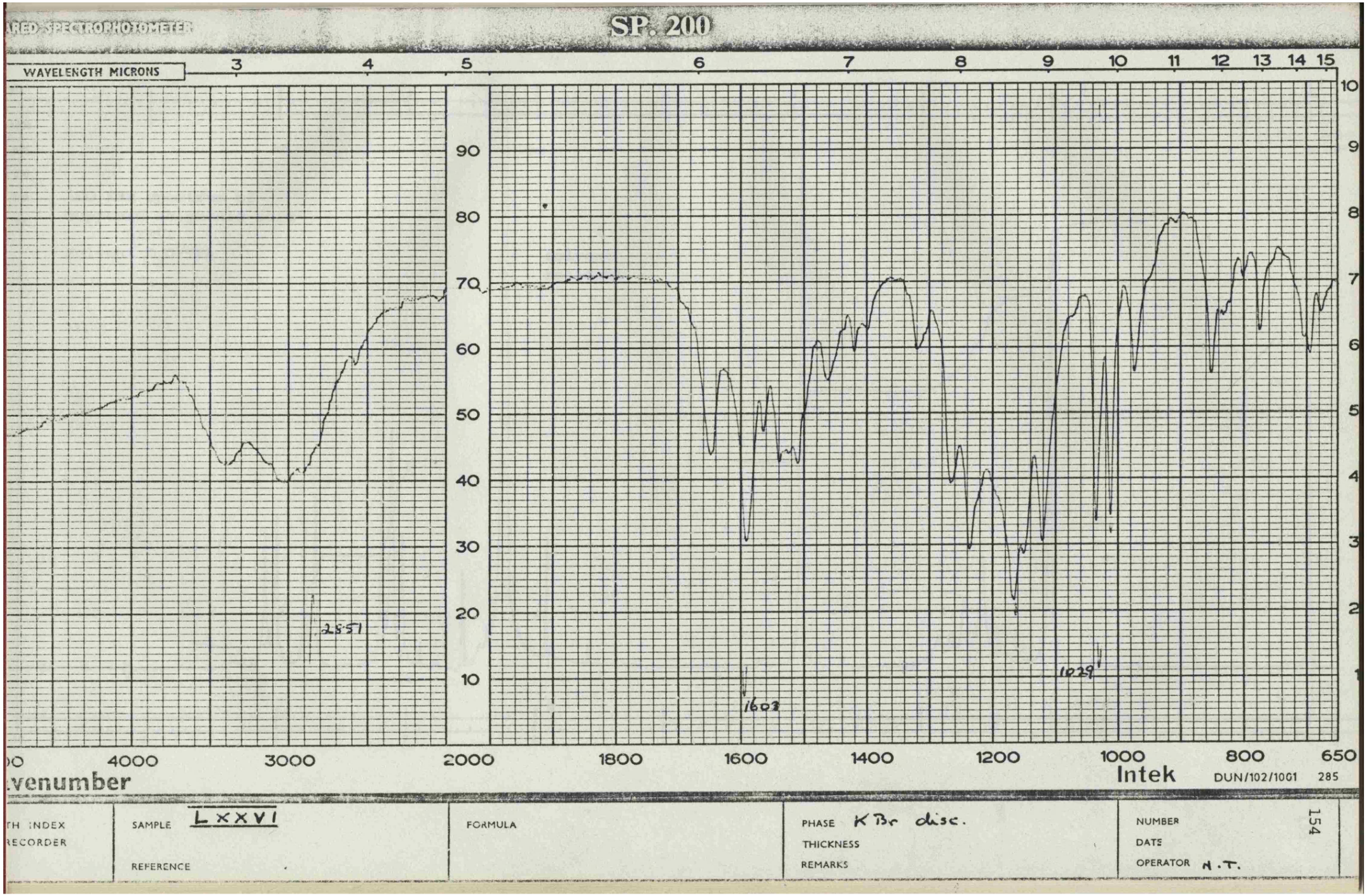

SPECTRUM NO.
DATE 30/1/26
FREQ.
NUCLEUS
SAMPLE
SOLVENT CDCl3
CONC. 15mgs
REFERENCE TMS
LOCK EXT
TEMP. RT °C
R. F. LEVEL 35
A.F. LEVEL
ANALYTICAL 3-8
LOCK
SD
AMPLITUDE
ANALYTICAL X10-3
LOCK
INTEGRATOR
FILTER 20
OFFSET Hz PPM
FREQ. FIELD FREQ. (FIELD)
MeO
Me
N
N
Me
OMe
LXV
HDO
after D2O
TMS
OPERATOR D. Wood
REMARKS;
SWEEP TIME (SEC.)
25 50 (100) (250) 500
1000 2500 5000 10000
SWEEP WIDTH (Hz)(X0.01PPM)
27 54 108 270 540
(1080) 2700 5400 10800
WIDE SWEEP (GAUSS)
10.8 27 54 108 540


MeO
OMe
OMe
N
O
LXVIII
SOLVENT CDCl3
TEMPERATURE ~30 °C
FREQ. RESPONSE 2 Hz
R.F. ATTENUATOR 30 db
SWEEP TIME 500 sec
SWEEP WIDTH 1000 Hz
SWEEP OFFSET — Hz
SPECTRUM AMP. 1000
LOCK SIGNAL TMS
FIELD MILLIGAUSS (MAN. OSC. FREQ.) 0.25 m.gauss
FIELD MILLIGAUSS (SWEEP FREQ.) 0.02 m.gauss
FIELD SWEEP ✓
FREQ. SWEEP □
τ 0 1 2 3 4 5 6 7 8 9
1000 500 250 100 50
400 300 200 100 0 Hz
10 9 8 7 6 5 4 3 2 1 0 δ


1000
500
250
100
50
400
300
200
100
0
H
Hz
SOLVENT
TEMPERATURE
FREQ. RESPONSE
R.F. ATTENUATOR
SWEEP TIME
SWEEP WIDTH
SWEEP OFFSET
SPECTRUM AMP.
LOCK SIGNAL
FIELD MILLIGAUSS (MAN. OSC. FREQ.)
FIELD MILLIGAUSS (SWEEP FREQ.)
FIELD SWEEP
FREQ. SWEEP
°C
Hz
db
sec
Hz
Hz
m.gauss
m.gauss
Me
O
NH
OMe

LXIX


Me
OMe
MeO
HN
OMe
LXXIV
after
deuteration
SOLVENT CDCl3
CONC. —
REFERENCE TMS
LOCK EXT
TEMP. 28 °C
R. F. LEVEL 40
A.F. LEVEL
ANALYTICAL 4-5
LOCK
SD
AMPLITUDE
ANALYTICAL x10-5
LOCK
INTEGRATOR
FILTER 20
OFFSET Hz PPM
FREQ. FIELD FREQ. FIELD
SPECTRUM NO.
DATE 13-8-75
FREQ.
NUCLEUS 1H
SAMPLE NT/CU/3
OPERATOR D. Wood
REMARKS:
SWEEP TIME SEC.
75 50 100 250 500
1000 2500 5000 10000
SWEEP WIDTH Hz X0.01PPM
27 54 108 270 540
1080 2700 5400 10800
WIDE SWEEP GAUSS
10 8 27 54 108 540


RED SPECTROPHOTOMETER
SP. 200
WAVELENGTH MICRONS
3
4
5
6
7
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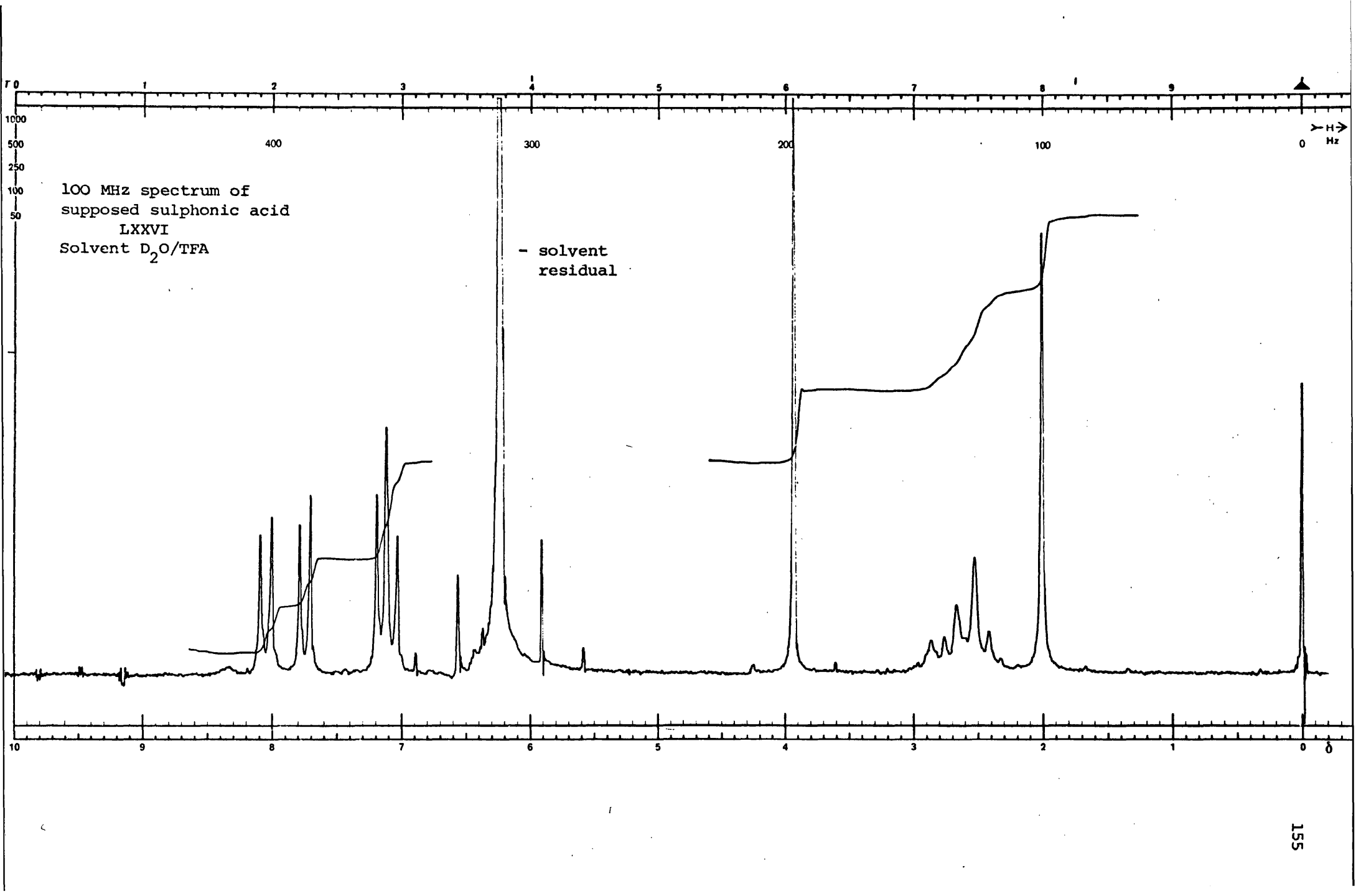
9
10
11
12
13
14
15
90
80
70
60
50
40
30
20
10
2851
1603
1029
4000
3000
2000
1800
1600
1400
1200
1000
800
650
venumber
Intek
DUN/102/1001
285
TH INDEX
RECORDER
SAMPLE LXXVI
REFERENCE
FORMULA
PHASE KBr disc.
THICKNESS
REMARKS
NUMBER 154
DATE
OPERATOR N.T.


100 MHz spectrum of
supposed sulphonic acid
LXXVI
Solvent D_2O/TFA
- solvent
residual
τ
δ
Hz

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